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A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis (UNIFI)

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2016 by Janssen Research & Development, LLC

Sponsor:
Janssen Research & Development, LLC

Information provided by (Responsible Party):
Janssen Research & Development, LLC

ClinicalTrials.gov Identifier:
NCT02407236

First received: March 30, 2015
Last updated: August 24, 2016
Last verified: August 2016
History of Changes

Purpose

The purpose of this study is to evaluate the efficacy and safety of ustekinumab as intravenous (IV: into the vein) infusion in induction study in participants with moderately to severely active Ulcerative Colitis (UC) and as subcutaneous (SC) administration in maintenance study in participants with moderately to severely active Ulcerative Colitis (UC) who have demonstrated a clinical response to Induction treatment with IV ustekinumab.

Condition	Intervention	Phase
Colitis, Ulcerative Inflammatory Bowel Diseases	Drug: Placebo IV Drug: Placebo SC Drug: Ustekinumab IV Drug: Ustekinumab SC	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)

Official Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis

Resource links provided by NLM:

Genetics Home Reference related topics: ulcerative colitis

MedlinePlus related topics: Ulcerative Colitis

Drug Information available for: Ustekinumab

U.S. FDA Resources

Further study details as provided by Janssen Research & Development, LLC:

Primary Outcome Measures:

- Induction Study - Number of Participants With Clinical Remission [Time Frame: Week 8] [Designated as safety issue: No]

  The global definition of Clinical remission is defined as Mayo score less than or equal to (<=) 2 points, with no individual subscore greater than (>) 1, for countries outside the United States (US). For the US, Clinical remission is defined as absolute stool number <=3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The Mayo score ranges from 0 to 12 points and consists of 4 subscores (stool frequency, rectal bleeding, findings on flexible sigmoidoscopy and physician's global assessment), each subscore is graded from 0 to 3 with the higher score indicating more severe disease activity.

- Maintenance Study - Number of Participants with Clinical Remission Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Week 44] [Designated as safety issue: No]

  The global definition of Clinical remission is defined as Mayo score less than or equal to (<=) 2 points, with no individual subscore greater than (>) 1, for countries

outside the United States (US). For the US Clinical remission is defined as absolute stool number <=3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. The Mayo score is a tool designed to measure disease activity for ulcerative colitis. The Mayo score ranges from 0 to 12 points and consists of 4 subscores (stool frequency, rectal bleeding, findings on flexible sigmoidoscopy and physician's global assessment), each subscore is graded from 0 to 3 with the higher score indicating more severe disease activity.

Secondary Outcome Measures:

- Induction Study - Number of Participants with Clinical Response [Time Frame: Week 8] [Designated as safety issue: No]

  Clinical response is defined as a decreased from Induction baseline in the Mayo score by greater than or equal to (>=) 30 percent (%) and >=3 points, with either a decrease from induction baseline in the rectal bleeding subscore >=1 or rectal bleeding subscore = 0 or 1.

- Induction Study - Number of Participants With Endoscopic Healing [Time Frame: Week 8] [Designated as safety issue: No]

  Endoscopic healing is improvement in the endoscopic appearance of the mucosa. It will be defined as Mayo endoscopic subscore = 0 or 1.

- Induction Study - Mean Change From Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Score [Time Frame: Week 8] [Designated as safety issue: No]

  The IBDQ is a 32-item questionnaire for participants with Inflammatory Bowel Disease (IBD) that will be used to evaluate the disease-specific health-related quality of life across 4 dimensional scores: bowel (loose stools, abdominal pain), systemic (fatigue, altered sleep pattern), social (work attendance, need to cancel social events), and emotional (anger, depression, irritability). The total score ranges from 32 to 224 with higher scores indicating better quality of life.

- Maintenance Study - Number of Participants with Clinical Response Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Through Week 44] [Designated as safety issue: No]

  Clinical response is defined as a decreased from Induction baseline in the Mayo score by greater than or equal to (>=) 30 percent (%) and >=3 points, with either a decrease from Induction baseline in the rectal bleeding subscore >=1 or rectal bleeding subscore = 0 or 1.

- Maintenance Study - Number of Participants with Endoscopic Healing Among Participants in Clinical Response to IV Ustekinumab Induction Treatment [Time Frame: Week 44] [Designated as safety issue: No]

  Endoscopic healing is improvement in the endoscopic appearance of the mucosa. It will be defined as Mayo endoscopic subscore = 0 or 1.

- Maintenance Study - Number of Participants with Clinical Remission Among those who Achieved Clinical Remission at Maintenance Study Baseline [Time Frame: Through Week 44] [Designated as safety issue: No]

  The global definition of Clinical remission is defined as Mayo score less than or equal to (<=) 2 points, with no individual subscore greater than (>) 1, for countries outside the United States (US). For the US Clinical remission is defined as absolute stool number <=3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. The Mayo score is a tool designed to measure disease activity for ulcerative colitis.

- Maintenance Study - Number of Participants with Clinical Remission and not Receiving Concomitant Corticosteroids Among those Receiving Concomitant Corticosteroids at Maintenance Baseline [Time Frame: Week 44] [Designated as safety issue: No]

  The global definition of Clinical remission is defined as Mayo score less than or equal to (<=) 2 points, with no individual subscore greater than (>) 1, for countries outside the United States (US). For the US Clinical remission is defined as absolute stool number <=3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. The Mayo score is a tool designed to measure disease activity for ulcerative colitis.

Estimated Enrollment:	951
Study Start Date:	July 2015
Estimated Study Completion Date:	July 2021
Estimated Primary Completion Date:	April 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Placebo Comparator: Induction Study - Placebo Intravenous (IV) Participants will be randomized to receive single dose of placebo as Intravenous (IV: into the vein) infusion at Week 0. Participants with clinical response at Week 8 will be eligible to enter the Maintenance study, but will not be randomized.	Drug: Placebo IV Placebo will be administered as intravenous infusion.
Experimental: Induction Study - Ustekinumab 130 milligram (mg) IV Participants will be randomized to receive single dose of ustekinumab 130 mg as IV infusion at Week 0. Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.	Drug: Ustekinumab IV Ustekinumab will be administered as intravenous infusion at Week 0 or Week 8 in Induction Study.
Experimental: Induction Study - Ustekinumab 6 mg/kg IV Participants will be randomized to receive ustekinumab approximating 6 mg/kg of body weight, as intravenous infusion at Week 0. Participants with clinical response at Week 8 will be eligible to enter the Maintenance study and will be randomized.	Drug: Ustekinumab IV Ustekinumab will be administered as intravenous infusion at Week 0 or Week 8 in Induction Study.
Induction Study- Placebo- Nonresponsders at Week 8 Participants without clinical response to placebo at Week 8 will receive a single IV infusion of ustekinumab approximating 6mg/kg along with matching subcutaneous (SC) placebo (to maintain the blind). Participants in clinical response at Week 16 will be eligible to enter Maintenance study and will be randomized.	Drug: Ustekinumab IV Ustekinumab will be administered as intravenous infusion at Week 0 or Week 8 in Induction Study.
Induction study-Ustekinumab Nonresponders at Week 8 Participants without clinical response to ustekinumab (130 mg or 6 mg/kg [IV]) at Week 8 will receive a single dose of ustekinumab 90 mg subcutaneously along with matching placebo intravenously (to maintain the blind). Participants in clinical response at Week 16 (that is, delayed responders) will be eligible to enter Maintenance study, but will not be randomized.	Drug: Ustekinumab SC Ustekinumab will be administered as subcutaneously.

Placebo Comparator: Maintenance Study - Placebo Subcutaneous (SC) Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive placebo subcutaneously, beginning Week 0 of Maintenance study through Week 44.	Drug: Placebo SC Placebo will be administered Subcutaneously.
Experimental: Maintenance Study - Ustekinumab 90mg SC every 12 weeks Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive ustekinumab 90 mg subcutaneously every 12 weeks, beginning Week 0 of Maintenance study through Week 44.	Drug: Ustekinumab SC Ustekinumab will be administered as subcutaneously.
Experimental: Maintenance Study - Ustekinumab 90mg SC every 8 weeks (q8w) Participants in clinical response (at Week 8 or Week 16) to Induction treatment with single IV infusion of Ustekinumab will be randomized to receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44.	Drug: Ustekinumab SC Ustekinumab will be administered as subcutaneously.
Maintenance Study - Placebo IV - Responder - Placebo SC Participants in clinical response to Induction treatment with IV Placebo will receive placebo subcutaneously, beginning Week 0 of Maintenance study through Week 44. Participants are not randomized.	Drug: Placebo SC Placebo will be administered Subcutaneously.
Maintenance Study-Delayed Responder-Ustekinumab 90mg SC q8w Participants without clinical response to induction treatment ustekinumab (130 mg or 6 mg/kg [IV]) at Week 8 but in clinical response at Week 16 after receiving Induction Ustekinumab at week 8 (delayed responders) will receive ustekinumab 90 mg subcutaneously every 8 weeks, beginning Week 0 of Maintenance study through Week 44. Participants are not randomized.	Drug: Ustekinumab SC Ustekinumab will be administered as subcutaneously.

Detailed Description:
This is a Phase 3, randomized (assignment of study drug by chance), double-blind (neither the participant or study staff will know the identity of study drugs), placebo-controlled (placebo is an inactive substance that is compared with a drug to test whether the drug has a real effect in a clinical trial), parallel-group (a medical research study comparing the response in 2 or more groups of participants receiving different interventions), multi-center (more than one clinical site will work on a medical research study), protocol of ustekinumab. The protocol will consist of 2 studies: an Induction study and a Maintenance study with unique endpoints. Screening period will be up to 8 Weeks. Induction study will be at least 8 weeks duration for each participant. Participant with clinical response in the Induction study will be eligible for the Maintenance study. The Maintenance study will be 44 weeks duration. After completion of the maintenance study, a long term extension will follow eligible participants for an additional 3 years. Clinical remission will be evaluated at Week 8 in the Induction study. Clinical remission among ustekinumab Induction responders will be evaluated at week 44 in the Maintenance study. Participants' safety will be monitored throughout.

Eligibility

Ages Eligible for Study: 18 Years and older (Adult, Senior)
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Has a clinical diagnosis of Ulcerative Colitis (UC) at least 3 months before Screening
- Has moderately to severely active UC, defined as a Baseline (Week 0) Mayo score of 6 to 12, including a Screening endoscopy subscore of the Mayo score greater than or equal to (>=) 2 as determined by a central reading of the video endoscopy
- Have failed biologic therapy, that is, have received treatment with 1 or more tumour necrosis factor (TNF) antagonists or vedolizumab at a dose approved for the treatment of UC, and have a documented history of failure to respond to or tolerate such treatment; OR Be naïve to biologic therapy (TNF antagonists or vedolizumab) or have received biologic therapy but have not demonstrated a history of failure to respond to, or tolerate, a biologic therapy and have a prior or current UC medication history that includes at least 1 of the following: a. Inadequate response to or failure to tolerate current treatment with oral corticosteroids or immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]) OR b. History of failure to respond to, or tolerate, at least 1 of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA) OR c. History of corticosteroid dependence (that is, an inability to successfully taper corticosteroids without a return of the symptoms of UC)
- Before the first administration of study agent, the following conditions must be met: vedolizumab must have been discontinued for at least 4 months and anti-tumor necrosis factors (TNFs) for at least 8 weeks

Exclusion Criteria:

- Has severe extensive colitis and is at imminent risk of colectomy
- Has UC limited to the rectum only or to < 20 centimeters (cm) of the colon
- Presence of a stoma or history of a fistula
- Participants with history of extensive colonic resection (for example, less than 30 cm of colon remaining) that would prevent adequate evaluation of the effect of study agent on clinical disease activity
- Participants with history of colonic mucosal dysplasia. Participants will not be excluded from the study because of a pathology finding of "indefinite dysplasia with reactive atypia"

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02407236

Contacts

Contact: Use link at the bottom of the page to see if you qualify for an enrolling site (see list). If you still have questions: JNJ.CT@sylogent.com

Show 301 Study Locations

Sponsors and Collaborators

Janssen Research & Development, LLC

Investigators

Study Director: Janssen Research & Development, LLC Clinical Trial Janssen Research & Development, LLC

More Information

Additional Information:

To learn how to participate in this trial please click here.

Responsible Party:	Janssen Research & Development, LLC
ClinicalTrials.gov Identifier:	NCT02407236 History of Changes
Other Study ID Numbers:	CR106920 2014-005606-38 CNTO1275UCO3001
Study First Received:	March 30, 2015
Last Updated:	August 24, 2016
Health Authority:	United States: Food and Drug Administration Canada: Health Canada Israel: Israeli Health Ministry Pharmaceutical Administration Russia: Ministry of Health of the Russian Federation Serbia: Medicines and Medical Devices Agency South Africa: Medicines Control Council Australia: Department of Health and Ageing Therapeutic Goods Administration South Korea: Ministry of Food and Drug Safety New Zealand: New Zealand Medicines and Medical Devices Safety Authority United Kingdom: Medicines and Healthcare Products Regulatory Agency Poland: Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczychul Hungary: National Institute of Pharmacy Germany: Paul-Ehrlich-Institut France: Agence Nationale de Sécurité du Médicament et des produits de santé Denmark: Danish Health and Medicines Authority Bulgaria: Bulgarian Drug Agency Austria: Bundesamt für Sicherheit im Gesundheitswesen Belgium: Agence Fédérale des Médicaments et Produits de Santé Czech Republic: Statni Ustav pro kontrolu leciv Italy: Agenzia Italiana del Farmaco Netherlands: Centrale Commissie Mensgebonden Onderzoek Romania: Agentia Nationala a Medicamentului si a Dispozitivelor Medicale Slovak Republic: Štátny ústav pre kontrolu liečiv

Keywords provided by Janssen Research & Development, LLC:
Ustekinumab
Inflammatory Bowel Diseases (IBD)
Colitis, Ulcerative

Additional relevant MeSH terms:

Ulcer	Gastroenteritis
Colitis, Ulcerative	Gastrointestinal Diseases
Colitis	Digestive System Diseases
Intestinal Diseases	Colonic Diseases
Inflammatory Bowel Diseases	Ustekinumab
Pathologic Processes	Dermatologic Agents

ClinicalTrials.gov processed this record on October 07, 2016

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Biologic License Application (BLA): 761044
Company: JANSSEN BIOTECH

EMAIL

Products on BLA 761044

CSV Excel Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
STELARA	USTEKINUMAB	130MG/26ML	INJECTABLE;INJECTION	Prescription	None	No	No

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for BLA 761044

Labels for BLA 761044

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
Language Assistance Available: Español | 繁體中文 | Tiếng Việt | 한국어 | Tagalog | Русский | العربية | Kreyòl Ayisyen | Français | Polski | Português | Italiano | Deutsch | 日本語 | فارسی | English

EXHIBIT B

https://web.archive.org/web/20150317160004/http://www.remicade.com/shared/product/remicade/prescribing-information.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REMICADE® safely and effectively. See full prescribing information for REMICADE.

REMICADE (infliximab)
Lyophilized Concentrate for Injection, for Intravenous Use
Initial U.S. Approval: 1998

WARNING: SERIOUS INFECTIONS and MALIGNANCY

See full prescribing information for complete boxed warning

SERIOUS INFECTIONS

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens.**
- **Discontinue REMICADE if a patient develops a serious infection.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting REMICADE. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

MALIGNANCY

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including REMICADE.**
- **Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including REMICADE. Almost all had received azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of REMICADE cases were reported in patients with Crohn's disease or ulcerative colitis, most of whom were adolescent or young adult males. (5.2)**

----------RECENT MAJOR CHANGES----------

WARNING: SERIOUS INFECTIONS and MALIGNANCY	01/2015
Warnings and Precautions: Serious Infections (5.1)	01/2015
Warnings and Precautions: Malignancies (5.2)	01/2015

----------INDICATIONS AND USAGE----------

REMICADE is a tumor necrosis factor (TNF) blocker indicated for:

Crohn's Disease (1.1):

- reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.

Pediatric Crohn's Disease (1.2):

- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Ulcerative Colitis (1.3):

- reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Pediatric Ulcerative Colitis (1.4):

- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Rheumatoid Arthritis (1.5) in combination with methotrexate:

- reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.

Ankylosing Spondylitis (1.6):

- reducing signs and symptoms in patients with active disease.

Psoriatic Arthritis (1.7):

- reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Plaque Psoriasis (1.8):

- treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

----------DOSAGE AND ADMINISTRATION----------

REMICADE is administered by intravenous infusion over a period of not less than 2 hours.

Crohn's Disease (2.1)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.

Pediatric Crohn's Disease (2.2)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Ulcerative Colitis (2.3)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Pediatric Ulcerative Colitis (2.4)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Rheumatoid Arthritis (2.5)

- In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.

Ankylosing Spondylitis (2.6)

- 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

Psoriatic Arthritis (2.7) and Plaque Psoriasis (2.8)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

----------DOSAGE FORMS AND STRENGTHS----------

100 mg of lyophilized infliximab in a 20 mL vial for intravenous infusion. (3)

----------CONTRAINDICATIONS----------

- REMICADE doses >5 mg/kg in moderate to severe heart failure. (4)
- Previous severe hypersensitivity reaction to REMICADE or known hypersensitivity to inactive components of REMICADE or to any murine proteins. (4)

----------WARNINGS AND PRECAUTIONS----------

- Serious infections – do not give REMICADE during an active infection. If an infection develops, monitor carefully and stop REMICADE if infection becomes serious. (5.1)
- Invasive fungal infections – for patients who develop a systemic illness on REMICADE, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic (5.1)
- Malignancies – the incidence of malignancies including lymphoma was greater in REMICADE treated patients than in controls. Due to the risk of HSTCL carefully assess the risk/benefit especially if the patient has Crohn's disease or ulcerative colitis, is male, and is receiving azathioprine or 6-mercaptopurine treatment. (5.2)
- Hepatitis B virus reactivation – test for HBV infection before starting REMICADE. Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop REMICADE and begin anti-viral therapy. (5.3)
- Hepatotoxicity – rare severe hepatic reactions, some fatal or necessitating liver transplantation. Stop REMICADE in cases of jaundice and/or marked liver enzyme elevations. (5.4)
- Heart failure – new onset or worsening symptoms may occur. (4, 5.5)
- Cytopenias – advise patients to seek immediate medical attention if signs and symptoms develop, and consider stopping REMICADE. (5.6)
- Hypersensitivity – serious infusion reactions including anaphylaxis or serum sickness-like reactions may occur. (5.7)
- Demyelinating disease – exacerbation or new onset may occur. (5.8)
- Lupus-like syndrome – stop REMICADE if syndrome develops. (5.13)
- Live vaccines or therapeutic infectious agents – should not be given with REMICADE. Bring pediatric patients up to date with all vaccinations prior to initiating REMICADE. (5.14)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>10%) – infections (e.g. upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Use with anakinra or abatacept– increased risk of serious infections (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric Use – REMICADE has not been studied in children with Crohn's disease or ulcerative colitis <6 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: January 2015

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REMICADE® (infliximab)

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCY

SERIOUS INFECTIONS

Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

REMICADE should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during therapy.[1,2] Treatment for latent infection should be initiated prior to REMICADE use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE *[see Warnings and Precautions (5.2)]*.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

1 INDICATIONS AND USAGE

1.1 Crohn's Disease

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

1.2 Pediatric Crohn's Disease

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

1.3 Ulcerative Colitis

REMICADE is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

1.4 Pediatric Ulcerative Colitis

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

1.5 Rheumatoid Arthritis

REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

1.6 Ankylosing Spondylitis

REMICADE is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

1.7 Psoriatic Arthritis

REMICADE is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

1.8 Plaque Psoriasis

REMICADE is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. REMICADE should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warnings, Warnings and Precautions (5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Crohn's Disease

The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of adults with moderately to severely active Crohn's disease or fistulizing Crohn's disease. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue REMICADE in these patients.

2.2 Pediatric Crohn's Disease

The recommended dose of REMICADE for pediatric patients 6 years and older with moderately to severely active Crohn's disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

2.3 Ulcerative Colitis

The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of adult patients with moderately to severely active ulcerative colitis.

2.4 Pediatric Ulcerative Colitis

The recommended dose of REMICADE for pediatric patients 6 years and older with moderately to severely active ulcerative colitis is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

2.5 Rheumatoid Arthritis

The recommended dose of REMICADE is 3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active rheumatoid arthritis. REMICADE should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses *[see Adverse Reactions (6.1)]*.

2.6 Ankylosing Spondylitis

The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks thereafter for the treatment of active ankylosing spondylitis.

2.7 Psoriatic Arthritis

The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of psoriatic arthritis. REMICADE can be used with or without methotrexate.

2.8 Plaque Psoriasis

The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of chronic severe (i.e., extensive and/or disabling) plaque psoriasis.

2.9 Monitoring to Assess Safety

Prior to initiating REMICADE and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection *[see Warnings and Precautions (5.1)]*.

2.10 Administration Instructions Regarding Infusion Reactions

Adverse effects during administration of REMICADE have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rashes. Anaphylaxis might occur at any time during REMICADE infusion. Approximately 20% of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared with 10% of placebo-treated patients *[see Adverse Reactions (6.1)]*. Prior to infusion with REMICADE, premedication may be administered at the physician's discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen and/or corticosteroids.

During infusion, mild to moderate infusion reactions may improve following slowing or suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids. For patients that do not tolerate the infusion following these interventions, REMICADE should be discontinued.

During or following infusion, patients who have severe infusion-related hypersensitivity reactions should be discontinued from further REMICADE treatment. The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

REMICADE® (infliximab)

2.11 General Considerations and Instructions for Preparation and Administration

REMICADE is intended for use under the guidance and supervision of a physician. The reconstituted infusion solution should be prepared by a trained medical professional using aseptic technique by the following procedure:

1. Calculate the dose, total volume of reconstituted REMICADE solution required and the number of REMICADE vials needed. Each REMICADE vial contains 100 mg of the infliximab antibody.
2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle as follows: Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if the lyophilized cake has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with sterile 0.9% Sodium Chloride Injection, USP, by withdrawing a volume equal to the volume of reconstituted REMICADE from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted REMICADE solution to the 250 mL infusion bottle or bag. Gently mix. The resulting infusion concentration should range between 0.4 mg/mL and 4 mg/mL.
4. The REMICADE infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE with other agents. REMICADE should not be infused concomitantly in the same intravenous line with other agents.
6. Parenteral drug products should be inspected visually before and after reconstitution for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

3 DOSAGE FORMS AND STRENGTHS

100 mg vial: 100 mg lyophilized infliximab in a 20 mL vial for injection, for intravenous use.

4 CONTRAINDICATIONS

REMICADE at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

REMICADE should not be re-administered to patients who have experienced a severe hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with REMICADE are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving REMICADE, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with REMICADE during treatment for latent tuberculosis.

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating REMICADE and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating REMICADE, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Tuberculosis should be strongly considered in patients who develop a new infection during REMICADE treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with REMICADE.

REMICADE should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with REMICADE should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive Fungal Infections

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

5.2 Malignancies

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

Lymphomas

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Hepatosplenic T-cell lymphoma (HSTCL)

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurrence of HSTCL is related to TNF-blockers or TNF-blockers in combination with these other immunosuppressants. When treating patients, consideration of whether to use REMICADE alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with REMICADE monotherapy from the clinical trial data *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1)]*.

Skin cancer

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including REMICADE *[see Adverse Reactions (6.2)]*. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Other Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking *[see Adverse Reactions (6.1)]*. Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD.

Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients with previous phototherapy *[see Adverse Reactions (6.1)]*.

The potential role of TNF-blocking therapy in the development of malignancies is not known *[see Adverse Reactions (6.1)]*. Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE.

5.3 Hepatitis B Virus Reactivation

Use of TNF blockers, including REMICADE, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients should be tested for HBV infection before initiating TNF blocker therapy, including REMICADE. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

5.4 Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury *[see Adverse Reactions (6.1)]*.

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5.5 Patients with Heart Failure

REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear *[see Contraindications (4) and Adverse Reactions (6.1)]*.

5.6 Hematologic Reactions

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities.

5.7 Hypersensitivity

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion.

However, in some cases, serum sickness-like reactions have been observed in patients after initial REMICADE therapy (i.e., as early as after the second dose), and when REMICADE therapy was reinstituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy.

REMICADE should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction *[see Adverse Reactions (6.1)]*.

In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, re-administration of REMICADE after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment *[see Adverse Reactions (6.1)]*. In general, the benefit-risk of re-administration of REMICADE after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2 and 6, should be carefully considered. In the case where REMICADE maintenance therapy for psoriasis is interrupted, REMICADE should be reinitiated as a single dose followed by maintenance therapy.

5.8 Neurologic Reactions

REMICADE and other agents that inhibit TNF have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of REMICADE in patients with these neurologic disorders and should consider discontinuation of REMICADE if these disorders develop.

5.9 Use with Anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended.

5.10 Use with Abatacept

In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Therefore, the combination of REMICADE and abatacept is not recommended *[see Drug Interactions (7.1)]*.

5.11 Concurrent Administration with other Biological Therapeutics

There is insufficient information regarding the concomitant use of REMICADE with other biological therapeutics used to treat the same conditions as REMICADE. The concomitant use of REMICADE with these biologics is not recommended because of the possibility of an increased risk of infection *[see Drug Interactions (7.3)]*.

REMICADE® (infliximab)

5.12 Switching between Biological Disease-Modifying Antirheumatic Drugs (DMARDs)

Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

5.13 Autoimmunity

Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued *[see Adverse Reactions (6.1)]*.

5.14 Live Vaccines/Therapeutic Infectious Agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections. It is recommended that live vaccines not be given concurrently with REMICADE. Caution is advised in the administration of live vaccines to infants born to female patients treated with REMICADE during pregnancy since REMICADE is known to cross the placenta and has been detected up to 6 months in the serum of infants born to female patients treated with REMICADE during pregnancy.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with REMICADE.

It is recommended that all pediatric patients be brought up to date with all vaccinations prior to initiating REMICADE therapy. The interval between vaccination and initiation of REMICADE therapy should be in accordance with current vaccination guidelines.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice.

Adverse Reactions in Adults

The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. *[For information on adverse reactions in pediatric patients see Adverse Reactions (6.1).]* One of the most-common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash).

Infusion-related Reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In phase 3 clinical studies, 18% of REMICADE-treated patients experienced an infusion reaction compared to 5% of placebo-treated patients. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 hour) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group.

Patients who became positive for antibodies to infliximab were more likely (approximately two- to three-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions *[see Adverse Reactions (6.1) and Drug Interactions (7.4)]*.

Infusion reactions following re-administration

In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction regimen of REMICADE following disease flare, 4% (8/219) of patients in the re-treatment therapy arm experienced serious infusion reactions versus < 1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive

any concomitant immunosuppressant therapy. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, REMICADE treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Reactions/Reactions Following Re-administration

In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within 2 weeks after repeat infusion.

Infections

In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE and may reflect recrudescence of latent disease *[see Warnings and Precautions (5.1)]*. In the 1-year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54-week Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess.

In REMICADE clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies.

The onset of serious infections may be preceded by constitutional symptoms such as fever, chills, weight loss, and fatigue. The majority of serious infections, however, may also be preceded by signs or symptoms localized to the site of the infection.

Autoantibodies/Lupus-like Syndrome

Approximately half of REMICADE-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Malignancies

In controlled trials, more REMICADE-treated patients developed malignancies than placebo-treated patients *[see Warnings and Precautions (5.2)]*.

In a randomized controlled clinical trial exploring the use of REMICADE in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these REMICADE-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51 - 14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head and neck.

Patients with Heart Failure

In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab. The assay used to measure anti-infliximab antibodies in patient samples is subject to interference by serum infliximab, possibly resulting in an underestimation of the rate of patient antibody formation. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. In a study of psoriatic arthritis in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction *[see Adverse Reactions (6.1)]* than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with REMICADE over the long term is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and they are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading.

Hepatotoxicity

Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE *[see Warnings and Precautions (5.4)]*. Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE, who are chronic carriers of this virus *[see Warnings and Precautions (5.3)]*.

In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls (Table 1), both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications.

Table 1 Proportion of patients with elevated ALT in clinical trials

	Proportion of patients with elevated ALT					
	>1 to <3 x ULN		≥3 x ULN		≥5 x ULN	
	Placebo	REMICADE	Placebo	REMICADE	Placebo	REMICADE
Rheumatoid arthritis[a]	24%	34%	3%	4%	<1%	<1%
Crohn's disease[b]	34%	39%	4%	5%	0%	2%
Ulcerative colitis[c]	12%	17%	1%	2%	<1%	<1%
Ankylosing spondylitis[d]	15%	51%	0%	10%	0%	4%
Psoriatic arthritis[e]	16%	50%	0%	7%	0%	2%
Plaque psoriasis[f]	24%	49%	<1%	8%	0%	3%

[a] Placebo patients received methotrexate while REMICADE patients received both REMICADE and methotrexate. Median follow-up was 58 weeks.

[b] Placebo patients in the 2 Phase 3 trials in Crohn's disease received an initial dose of 5 mg/kg REMICADE at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT analysis. Median follow-up was 54 weeks.

[c] Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for REMICADE.

[d] Median follow-up was 24 weeks for the placebo group and 102 weeks for the REMICADE group.

[e] Median follow-up was 39 weeks for the REMICADE group and 18 weeks for the placebo group.

[f] ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and 16 weeks for placebo.

Adverse Reactions in Psoriasis Studies

During the placebo-controlled portion across the 3 clinical trials up to week 16, the proportion of patients who experienced at least 1 serious adverse reaction (SAE; defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 0.5% in the 3 mg/kg REMICADE group, 1.9% in the placebo group, and 1.6% in the 5 mg/kg REMICADE group.

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Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE.

One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting REMICADE.

In the placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo.

In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints, and immobility.

Other Adverse Reactions

Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions. *[For information on other adverse reactions in pediatric patients, see Adverse Reactions (6.1)].* Adverse reactions reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.

Table 2 Adverse reactions occurring in 5% or more of patients receiving 4 or more infusions for rheumatoid arthritis

	Placebo	REMICADE
	(n=350)	(n=1129)
Average weeks of follow-up	59	66
Gastrointestinal		
Nausea	20%	21%
Abdominal pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Skin and appendages disorders		
Rash	5%	10%
Pruritus	2%	7%
Body as a whole-general disorders		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

The most common serious adverse reactions observed in clinical trials were infections *[see Adverse Reactions (6.1)].* Other serious, medically relevant adverse reactions ≥0.2% or clinically significant adverse reactions by body system were as follows:

Body as a whole: allergic reaction, edema
Blood: pancytopenia
Cardiovascular: hypotension
Gastrointestinal: constipation, intestinal obstruction

REMICADE® (infliximab)

Central and Peripheral Nervous: dizziness
Heart Rate and Rhythm: bradycardia
Liver and Biliary: hepatitis
Metabolic and Nutritional: dehydration
Platelet, Bleeding and Clotting: thrombocytopenia
Neoplasms: lymphoma
Red Blood Cell: anemia, hemolytic anemia
Resistance Mechanism: cellulitis, sepsis, serum sickness, sarcoidosis
Respiratory: lower respiratory tract infection (including pneumonia), pleurisy, pulmonary edema
Skin and Appendages: increased sweating
Vascular (Extracardiac): thrombophlebitis
White Cell and Reticuloendothelial: leukopenia, lymphadenopathy

Adverse Reactions in Pediatric Patients

Pediatric Crohn's Disease

There were some differences in the adverse reactions observed in the pediatric patients receiving REMICADE compared to those observed in adults with Crohn's disease. These differences are discussed in the following paragraphs.

The following adverse reactions were reported more commonly in 103 randomized pediatric Crohn's disease patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult Crohn's disease patients receiving a similar treatment regimen: anemia (11%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8-week as opposed to every 12-week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8-week and 4 patients in the every 12-week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8-week and 1 in the every 12-week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group.

In Study Peds Crohn's, 18% of randomized patients experienced 1 or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.

In Study Peds Crohn's, in which all patients received stable doses of 6-MP, AZA, or MTX, excluding inconclusive samples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in Crohn's disease clinical trials; 4% had ALT elevations ≥3 x ULN, and 1% had elevations ≥5 x ULN. (Median follow-up was 53 weeks.)

Pediatric Ulcerative Colitis

Overall, the adverse reactions reported in the pediatric ulcerative colitis trial and adult ulcerative colitis (Study UC I and Study UC II) studies were generally consistent. In a pediatric UC trial, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache.

Infections were reported in 31 (52%) of 60 treated patients in the pediatric UC trial and 22 (37%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in the pediatric UC trial was similar to that in the pediatric Crohn's disease study (Study Peds Crohn's) but higher than the proportion in the adults' ulcerative colitis studies (Study UC I and Study UC II). The overall incidence of infections in the pediatric UC trial was 13/22 (59%) in the every 8 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients.

In the pediatric UC trial, excluding inconclusive samples, 4 of 19 patients had antibodies to infliximab. Although 52 patients were tested, 33 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 17% (10/60) of pediatric patients in the pediatric UC trial; 7% (4/60) had ALT elevations ≥3 x ULN, and 2% (1/60) had elevations ≥5 x ULN (median follow-up was 49 weeks).

Overall, 8 of 60 (13%) treated patients experienced one or more infusion reactions, including 4 of 22 (18%) patients in the every 8-week treatment maintenance group. No serious infusion reactions were reported.

In the pediatric UC trial, 45 patients were in the 12 to 17 year age group and 15 in the 6 to 11 year age group. The numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events. There were higher proportions of patients with serious adverse events (40% vs. 18%) and discontinuation due to adverse events (40% vs. 16%) in the younger age group than in the older age group. While the proportion of patients with infections was also

higher in the younger age group (60% vs. 49%), for serious infections, the proportions were similar in the two age groups (13% in the 6 to 11 year age group vs. 11% in the 12 to 17 year age group). Overall proportions of adverse reactions, including infusion reactions, were similar between the 6 to 11 and 12 to 17 year age groups (13%).

6.2 Post-marketing Experience

Adverse reactions have been reported during post approval use of REMICADE in adult and pediatric patients. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure.

The following adverse reactions, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia *[see Warnings and Precautions (5.6)]*, interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), transverse myelitis, and neuropathies (additional neurologic reactions have also been observed) *[see Warnings and Precautions (5.8)]*, acute liver failure, jaundice, hepatitis, and cholestasis *[see Warnings and Precautions (5.4)]*, serious infections *[see Warnings and Precautions (5.1)]* and malignancies, including melanoma and Merkel cell carcinoma *[see Warnings and Precautions (5.2)]*.

Infusion-related Reactions

In post-marketing experience, cases of anaphylactic reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with REMICADE administration.

Cases of myocardial ischemia/infarction and transient visual loss have also been rarely reported in association with REMICADE during or within 2 hours of infusion.

Adverse Reactions in Pediatric Patients

The following serious adverse reactions have been reported in the post-marketing experience in children: infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions.

Serious adverse reactions in the post-marketing experience with REMICADE in the pediatric population have also included malignancies, including hepatosplenic T-cell lymphomas *[see Boxed WARNINGS and Warnings and Precautions (5.2)]*, transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies.

7 DRUG INTERACTIONS

7.1 Use with Anakinra or Abatacept

An increased risk of serious infections was seen in clinical studies of other TNFα-blocking agents used in combination with anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNF-blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra or abatacept is not recommended *[see Warnings and Precautions (5.9 and 5.10)]*.

7.2 Use with Tocilizumab

The use of tocilizumab in combination with biological DMARDs such as TNF antagonists, including REMICADE, should be avoided because of the possibility of increased immunosuppression and increased risk of infection.

7.3 Use with Other Biological Therapeutics

The combination of REMICADE with other biological therapeutics used to treat the same conditions as REMICADE is not recommended *[see Warnings and Precautions (5.11)]*.

7.4 Methotrexate (MTX) and Other Concomitant Medications

Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-infliximab antibody production and increase infliximab concentrations.

7.5 Immunosuppressants

Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants *[see Adverse Reactions (6.1)]*. Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

7.6 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of REMICADE in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

7.7 Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with REMICADE *[see Warnings and Precautions (5.14)]*.

It is recommended that therapeutic infectious agents not be given concurrently with REMICADE *[see Warnings and Precautions (5.14)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed. Because infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

As with other IgG antibodies, REMICADE crosses the placenta and has been detected up to 6 months in the serum of infants born to female patients treated with REMICADE during pregnancy. Consequently, these infants may be at increased risk of infection, and caution is advised in the administration of live vaccines to these infants *[see Warnings and Precautions (5.14)]*.

8.3 Nursing Mothers

It is not known whether REMICADE is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE, women should not breast-feed their infants while taking REMICADE. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of REMICADE have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of Crohn's disease or ulcerative colitis. However, REMICADE has not been studied in children with Crohn's disease or ulcerative colitis <6 years of age.

Pediatric Crohn's Disease

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy *[see Boxed Warnings, Warnings and Precautions (5), Indications and Usage (1.2), Dosage and Administration (2.2), Clinical Studies (14.2) and Adverse Reactions (6.1)]*.

REMICADE has been studied only in combination with conventional immunosuppressive therapy in pediatric Crohn's disease. The longer term (greater than 1 year) safety and effectiveness of REMICADE in pediatric Crohn's disease patients have not been established in clinical trials.

Pediatric Ulcerative Colitis

The safety and effectiveness of REMICADE for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of REMICADE in adults. Additional safety and pharmacokinetic data were collected in 60 pediatric patients aged 6 years and older *[see Clinical Pharmacology (12.3), Dosage and Administration (2.4), Adverse Reactions (6.1), and Clinical Studies (14.4)]*. The effectiveness of REMICADE in inducing and maintaining mucosal healing could not be established. Although 41 patients had a Mayo endoscopy subscore of 0 or 1 at the Week 8 endoscopy, the induction phase was open-label and lacked a control group. Only 9 patients had an optional endoscopy at Week 54.

In the pediatric UC trial, approximately half of the patients were on concomitant immunomodulators (AZA, 6-MP, MTX) at study start. Due to the risk of HSTCL, a careful risk-benefit assessment should be made when REMICADE is used in combination with other immunosuppressants.

The longer term (greater than 1 year) safety and effectiveness of REMICADE in pediatric ulcerative colitis patients have not been established in clinical trials.

Juvenile Rheumatoid Arthritis (JRA)

The safety and efficacy of REMICADE in patients with juvenile rheumatoid arthritis (JRA) were evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤0.2 mg/kg/day of prednisone or equivalent), NSAIDs, and/or disease modifying antirheumatic drugs (DMARDs) was permitted.

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Doses of 3 mg/kg REMICADE or placebo were administered intravenously at Weeks 0, 2 and 6. Patients randomized to placebo crossed-over to receive 6 mg/kg REMICADE at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with REMICADE for up to 2 years in a companion extension study.

The study failed to establish the efficacy of REMICADE in the treatment of JRA. Key observations in the study included a high placebo response rate and a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance of infliximab was observed than had been observed in adults *[see Clinical Pharmacology (12.3)]*.

A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg REMICADE was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious infusion reaction, 1 of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received REMICADE by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg REMICADE compared with 12% (6/49) of patients who received 6 mg/kg.

A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg REMICADE in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient.

8.5 Geriatric Use

In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older who received REMICADE, compared to younger patients—although the incidence of serious adverse reactions in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. There is a greater incidence of infections in the elderly population in general. The incidence of serious infections in REMICADE-treated patients 65 years and older was greater than in those under 65 years of age; therefore caution should be used in treating the elderly *[see Adverse Reactions (6.1)]*.

10 OVERDOSAGE

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

Infliximab, the active ingredient in REMICADE, is a chimeric IgG1κ monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNFα). It has a molecular weight of approximately 149.1 kilodaltons. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* or *in vivo*. Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

12.2 Pharmacodynamics

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In rheumatoid arthritis, treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with REMICADE reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with REMICADE, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from REMICADE-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with REMICADE resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In plaque psoriasis, REMICADE treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which REMICADE exerts its clinical effects is unknown.

12.3 Pharmacokinetics

In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of REMICADE, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with Crohn's disease or ulcerative colitis following the administration of 5 mg/kg infliximab.

Population pharmacokinetic analysis showed that in children with juvenile rheumatoid arthritis (JRA) with a body weight of up to 35 kg receiving 6 mg/kg REMICADE and children with JRA with body weight greater than 35 kg up to adult body weight receiving 3 mg/kg REMICADE, the steady state area under the concentration curve (AUC_{ss}) was similar to that observed in adults receiving 3 mg/kg of REMICADE.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

14 CLINICAL STUDIES

14.1 Crohn's Disease

Active Crohn's Disease

The safety and efficacy of single and multiple doses of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's disease [Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 400] with an inadequate response to prior conventional

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therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at Week 4 vs. 81% (22/27) of patients receiving 5 mg/kg REMICADE (p<0.001, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission (CDAI<150) at Week 4.

In a multidose trial (ACCENT I [Study Crohn's I]), 545 patients received 5 mg/kg at Week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at Weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at Week 2 were randomized and analyzed separately from those not in response at Week 2. Corticosteroid taper was permitted after Week 6.

At Week 2, 57% (311/545) of patients were in clinical response. At Week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 3).

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg REMICADE maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at Week 54 (Table 3).

Table 3 Clinical remission and steroid withdrawal

	Single 5-mg/kg Dose[a]	Three-Dose Induction[b]	
	Placebo Maintenance	REMICADE Maintenance q 8 wks	
		5 mg/kg	10 mg/kg
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
P-value[c]		0.022	0.001
Week 54			
Patients in remission able to discontinue corticosteroid use[d]	6/54 11%	14/56 25%	18/53 34%
P-value[c]		0.059	0.005

[a] REMICADE at Week 0
[b] REMICADE 5 mg/kg administered at Weeks 0, 2 and 6
[c] *P*-values represent pairwise comparisons to placebo
[d] Of those receiving corticosteroids at baseline

Patients in the REMICADE maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 1). At Weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg REMICADE-treated groups compared to the placebo group in the disease-specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

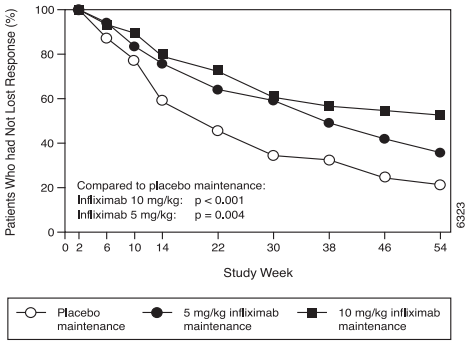


Figure 1 Kaplan-Meier estimate of the proportion of patients who had not lost response through Week 54

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in the REMICADE maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at Week 10. Of the REMICADE-treated patients showing mucosal healing at Week 10, 9 of 12 patients also showed mucosal healing at Week 54.

Patients who achieved a response and subsequently lost response were eligible to receive REMICADE on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at Week 2, 59% (92/157) of REMICADE maintenance patients responded by Week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by Week 14, additional therapy did not result in significantly more responses *[see Dosage and Administration (2)]*.

Fistulizing Crohn's Disease

The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates, antibiotics, MTX, 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.

In the first trial, 94 patients received 3 doses of either placebo or REMICADE at Weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least 2 consecutive visits without an increase in medication or surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE group (*P*=0.002) and 56% (18/32) of patients in the 10 mg/kg REMICADE group (*P*=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% of REMICADE-treated patients compared with 13% of placebo-treated patients (*P*<0.001).

In the second trial (ACCENT II [Study Crohn's II]), patients who were enrolled had to have at least 1 draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg REMICADE at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg REMICADE maintenance at Week 14. Patients received maintenance doses at Week 14 and then every 8 weeks through Week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both Weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.

At Week 14, 65% (177/273) of patients were in fistula response. Patients randomized to REMICADE maintenance had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 2). At Week 54, 38% (33/87) of REMICADE-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (*P*=0.02). Compared to placebo maintenance, patients on REMICADE maintenance had a trend toward fewer hospitalizations.

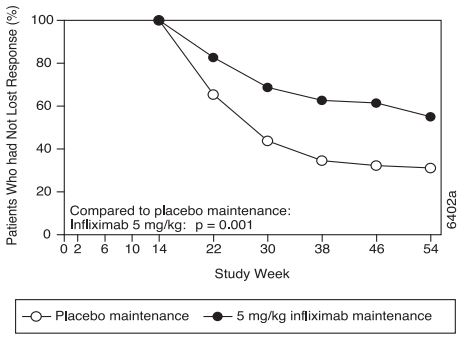


Figure 2 Life table estimates of the proportion of patients who had not lost fistula response through Week 54

Patients who achieved a fistula response and subsequently lost response were eligible to receive REMICADE maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg REMICADE, and 57% (12/21) of REMICADE maintenance patients responded to 10 mg/kg.

Patients who had not achieved a response by Week 14 were unlikely to respond to additional doses of REMICADE.

Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

14.2 Pediatric Crohn's Disease

The safety and efficacy of REMICADE were assessed in a randomized, open-label study (Study Peds Crohn's) in 112 pediatric patients aged 6 to 17 years old with moderately to severely active Crohn's disease and an inadequate response to conventional therapies. The median age was 13 years and the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 (on a scale of 0 to 100). All patients were required to be on a stable dose of 6-MP, AZA, or MTX; 35% were also receiving corticosteroids at baseline.

All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given either every 8 weeks or every 12 weeks.

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At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥15 points and total PCDAI score of ≤ 30 points), and 59% were in clinical remission (defined as PCDAI score of ≤10 points).

The proportion of pediatric patients achieving clinical response at Week 10 compared favorably with the proportion of adults achieving a clinical response in Study Crohn's I. The study definition of clinical response in Study Peds Crohn's was based on the PCDAI score, whereas the CDAI score was used in the adult Study Crohn's I.

At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the every 8-week treatment group than in the every 12-week treatment group (73% vs. 47% at Week 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in clinical remission was also greater in the every 8-week treatment group than in the every 12-week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54), (Table 4).

For patients in Study Peds Crohn's receiving corticosteroids at baseline, the proportion of patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every 8-week maintenance group and 33% for the every 12-week maintenance group. At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for the every 8-week maintenance group and 17% for the every 12-week maintenance group.

Table 4 Response and remission in study peds Crohn's

	5 mg/kg REMICADE	
	Every 8 Week	Every 12 Week
	Treatment Group	Treatment Group
Patients randomized	52	51
Clinical Response[a]		
Week 30	73%[d]	47%
Week 54	64%[d]	33%
Clinical Remission[b]		
Week 30	60%[c]	35%
Week 54	56%[d]	24%

[a] Defined as a decrease from baseline in the PCDAI score of ≥15 points and total score of ≤ 30 points.
[b] Defined as a PCDAI score of ≤ 10 points.
[c] *P*-value <0.05
[d] *P*-value <0.01

14.3 Ulcerative Colitis

The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative colitis (UC) (Mayo score[5] 6 to 12 [of possible range 0 to 12], Endoscopy subscore ≥2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Corticosteroid taper was permitted after Week 8. Patients were randomized at week 0 to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46 in Study UC I, and at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 22 in Study UC II. In Study UC II, patients were allowed to continue blinded therapy to Week 46 at the investigator's discretion.

Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-MP, or AZA. Patients in Study UC II had failed to respond or were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-MP/AZA (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%, respectively). Clinical response was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Clinical Response, Clinical Remission, and Mucosal Healing

In both Study UC I and Study UC II, greater percentages of patients in both REMICADE groups achieved clinical response, clinical remission and mucosal healing than in the placebo group. Each of these effects was maintained through the end of each trial (Week 54 in Study UC I, and Week 30 in Study UC II). In addition, a greater proportion of patients in REMICADE groups demonstrated sustained response and sustained remission than in the placebo groups (Table 5).

Of patients on corticosteroids at baseline, greater proportions of patients in the REMICADE treatment groups were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the patients in the placebo treatment groups (22% in REMICADE treatment groups vs. 10% in placebo group in Study UC I; 23% in REMICADE treatment groups vs. 3% in placebo group in Study UC II). In Study UC I, this effect was maintained through Week 54 (21% in REMICADE treatment groups vs. 9% in placebo group). The REMICADE-associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

REMICADE® (infliximab)

Table 5 Response, remission and mucosal healing in ulcerative colitis studies

	Study UC I			Study UC II		
	Placebo	5 mg/kg REMICADE	10 mg/kg REMICADE	Placebo	5 mg/kg REMICADE	10 mg/kg REMICADE
Patients randomized	121	121	122	123	121	120
Clinical Response[a, d]						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%**	26%	47%*	60%*
Week 54	20%	45%*	44%*	NA	NA	NA
Sustained Response[d] (Clinical response at both Week 8 and 30)	23%	49%*	46%*	15%	41%*	53%*
(Clinical response at Weeks 8, 30, and 54)	14%	39%*	37%*	NA	NA	NA
Clinical Remission[b, d]						
Week 8	15%	39%*	32%**	6%	34%*	28%*
Week 30	16%	34%**	37%*	11%	26%**	36%*
Week 54	17%	35%**	34%**	NA	NA	NA
Sustained Remission[d] (Clinical remission at both Week 8 and 30)	8%	23%**	26%*	2%	15%*	23%*
(Clinical remission at Weeks 8, 30 and 54)	7%	20%**	20%**	NA	NA	NA
Mucosal Healing[c, d]						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%*	49%*	30%	46%**	57%*
Week 54	18%	45%*	47%*	NA	NA	NA

* $P < 0.001$, ** $P < 0.01$
[a] Defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings.)
[b] Defined as a Mayo score ≤ 2 points, no individual subscore >1.
[c] Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.
[d] Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the time of the event onward.

The improvement with REMICADE was consistent across all Mayo subscores through Week 54 (Study UC I shown in Table 6; Study UC II through Week 30 was similar).

Table 6 Proportion of patients in Study UC I with Mayo subscores indicating inactive or mild disease through Week 54

	Study UC I		
		REMICADE	
	Placebo	**5 mg/kg**	**10 mg/kg**
	(n=121)	(n=121)	(n=122)
Stool frequency			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
Week 54	31%	52%	51%
Rectal bleeding			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
Week 54	62%	69%	67%
Physician's Global Assessment			
Baseline	4%	6%	3%
Week 8	44%	74%	64%
Week 30	36%	57%	55%
Week 54	26%	53%	53%
Endoscopy findings			
Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%
Week 54	21%	50%	51%

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14.4 Pediatric Ulcerative Colitis

The safety and effectiveness of REMICADE for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of REMICADE in adults. Additional safety and pharmacokinetic data were collected in an open-label pediatric UC trial in 60 pediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12; Endoscopic subscore ≥ 2) and an inadequate response to conventional therapies. At baseline, the median Mayo score was 8, 53% of patients were receiving immunomodulator therapy (6-MP/AZA/MTX), and 62% of patients were receiving corticosteroids (median dose 0.5 mg/kg/day in prednisone equivalents). Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.

All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. Patients who did not respond to REMICADE at Week 8 received no further REMICADE and returned for safety follow-up. At Week 8, 45 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given either every 8 weeks through Week 46 or every 12 weeks through Week 42. Patients were allowed to change to a higher dose and/or more frequent administration schedule if they experienced loss of response.

Clinical response at Week 8 was defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, including a decrease in the rectal bleeding subscore by ≥ 1 points or achievement of a rectal bleeding subscore of 0 or 1.

Clinical remission at Week 8 was measured by the Mayo score, defined as a Mayo score of ≤ 2 points with no individual subscore >1. Clinical remission was also assessed at Week 8 and Week 54 using the Pediatric Ulcerative Colitis Activity Index (PUCAI)[6] score and was defined by a PUCAI score of <10 points.

Endoscopies were performed at baseline and at Week 8. A Mayo endoscopy subscore of 0 indicated normal or inactive disease and a subscore of 1 indicated mild disease (erythema, decreased vascular pattern, or mild friability).

Of the 60 patients treated, 44 were in clinical response at Week 8. Of 32 patients taking concomitant immunomodulators at baseline, 23 achieved clinical response at Week 8, compared to 21 of 28 of those not taking concomitant immunomodulators at baseline. At Week 8, 24 of 60 patients were in clinical remission as measured by the Mayo score and 17 of 51 patients were in remission as measured by the PUCAI score.

At Week 54, 8 of 21 patients in the every 8-week maintenance group and 4 of 22 patients in the every 12-week maintenance group achieved remission as measured by the PUCAI score.

During maintenance phase, 23 of 45 randomized patients (9 in the every 8-week group and 14 in the every 12-week group) required an increase in their dose and/or increase in frequency of REMICADE administration due to loss of response. Nine of the 23 patients who required a change in dose had achieved remission at Week 54. Seven of those patients received the 10 mg/kg every 8-week dosing.

14.5 Rheumatoid Arthritis

The safety and efficacy of REMICADE were assessed in 2 multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤ 10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted.

Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of REMICADE + MTX: 3 mg/kg or 10 mg/kg of REMICADE by IV infusion at Weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.

Study RA II was a placebo-controlled study of 3 active treatment arms in 1004 MTX naive patients of 3 or fewer years' duration active rheumatoid arthritis. Patients enrolled had a median age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At randomization, all patients received MTX (optimized to 20 mg/wk by Week 8) and either placebo, 3 mg/kg or 6 mg/kg REMICADE at Weeks 0, 2, and 6 and every 8 weeks thereafter.

Data on use of REMICADE without concurrent MTX are limited *[see Adverse Reactions (6.1)]*.

Clinical response

In Study RA I, all doses/schedules of REMICADE + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 7). This improvement was observed at Week 2 and maintained through Week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with REMICADE + MTX compared to placebo + MTX (Table 8). More patients treated with REMICADE reached a major clinical response than placebo-treated patients (Table 7).

In Study RA II, after 54 weeks of treatment, both doses of REMICADE + MTX resulted in statistically significantly greater response in signs and symptoms compared to MTX alone as measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 7). More patients treated with REMICADE reached a major clinical response than placebo-treated patients (Table 7).

Table 7 ACR response (percent of patients)

	Study RA I					Study RA II		
		REMICADE + MTX					REMICADE + MTX	
		3 mg/kg		10 mg/kg			3 mg/kg	6 mg/kg
Response	Placebo + MTX (n=88)	q 8 wks (n=86)	q 4 wks (n=86)	q 8 wks (n=87)	q 4 wks (n=81)	Placebo + MTX (n=274)	q 8 wks (n=351)	q 8 wks (n=355)
ACR 20								
Week 30	20%	50%[a]	50%[a]	52%[a]	58%[a]	N/A	N/A	N/A
Week 54	17%	42%[a]	48%[a]	59%[a]	59%[a]	54%	62%[c]	66%[a]
ACR 50								
Week 30	5%	27%[a]	29%[a]	31%[a]	26%[a]	N/A	N/A	N/A
Week 54	9%	21%[c]	34%[a]	40%[a]	38%[a]	32%	46%[a]	50%[a]
ACR 70								
Week 30	0%	8%[b]	11%[b]	18%[a]	11%[a]	N/A	N/A	N/A
Week 54	2%	11%[c]	18%[a]	26%[a]	19%[a]	21%	33%[b]	37%[a]
Major clinical response[#]	0%	7%[c]	8%[b]	15%[a]	6%[c]	8%	12%	17%[a]

\# A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through week 102 for Study RA I and week 54 for Study RA II.

[a] $P \leq 0.001$

[b] $P < 0.01$

[c] $P < 0.05$

Table 8 Components of ACR 20 at baseline and 54 weeks (Study RA I)

	Placebo + MTX (n=88)		REMICADE + MTX[a] (n=340)	
Parameter (medians)	Baseline	Week 54	Baseline	Week 54
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain[b]	6.7	6.1	6.8	3.3
Physician's Global Assessment[b]	6.5	5.2	6.2	2.1
Patient's Global Assessment[b]	6.2	6.2	6.3	3.2
Disability Index (HAQ-DI)[c]	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

[a] All doses/schedules of REMICADE + MTX

[b] Visual Analog Scale (0=best, 10=worst)

[c] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Radiographic response

Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.[3]

In Study RA I, approximately 80% of patients had paired X-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 9) and maintained through 102 weeks.

In Study RA II, >90% of patients had at least 2 evaluable X-rays. Inhibition of progression of structural damage was observed at Weeks 30 and 54 (Table 9) in the REMICADE + MTX groups compared to MTX alone. Patients treated with REMICADE + MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute-phase reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute-phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units compared to patients treated with REMICADE + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units compared to REMICADE + MTX who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had no progression (vdH-S score ≤ 0 unit) of structural damage compared to 45% of patients receiving MTX alone. In a subset of patients who began the study without erosions, REMICADE + MTX maintained an erosion-free state at 1 year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively (P<0.01). Fewer patients in the REMICADE + MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).

Table 9 Radiographic change from baseline to Week 54

	Study RA I			Study RA II		
		REMICADE + MTX			REMICADE + MTX	
		3 mg/kg	10 mg/kg		3 mg/kg	6 mg/kg
	Placebo + MTX (n=64)	q 8 wks (n=71)	q 8 wks (n=77)	Placebo + MTX (n=282)	q 8 wks (n=359)	q 8 wks (n=363)
Total Score						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3[a]	0.2[a]	3.7	0.4[a]	0.5[a]
Median	4.0	0.5	0.5	0.4	0.0	0.0
Erosion Score						
Baseline						
Mean	44	44	33	8.3	8.8	8.3
Median	25	29	22	3.0	3.8	3.8
Change from baseline						
Mean	4.1	0.2[a]	0.2[a]	3.0	0.3[a]	0.1[a]
Median	2.0	0.0	0.5	0.3	0.0	0.0
JSN Score						
Baseline						
Mean	36	34	31	3.0	2.9	2.9
Median	26	29	24	1.0	1.0	1.0
Change from baseline						
Mean	2.9	1.1[a]	0.0[a]	0.6	0.1[a]	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

[a] P <0.001 for each outcome against placebo.

Physical function response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

In Study RA I, all doses/schedules of REMICADE + MTX showed significantly greater improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged over time through Week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score. The median (interquartile range) improvement from baseline to Week 54 in HAQ-DI was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for REMICADE + MTX (p<0.001). Both HAQ-DI and SF-36 effects were maintained through Week 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in the trial through 102 weeks.

In Study RA II, both REMICADE treatment groups showed greater improvement in HAQ-DI from baseline averaged over time through Week 54 compared to MTX alone; 0.7 for REMICADE + MTX vs. 0.6 for MTX alone ($P \leq 0.001$). No worsening in the SF-36 mental component summary score was observed.

14.6 Ankylosing Spondylitis

The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New York criteria for Ankylosing Spondylitis.[4] Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18.

At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo group (p<0.001). Improvement was observed at Week 2 and maintained through Week 24 (Figure 3 and Table 10).

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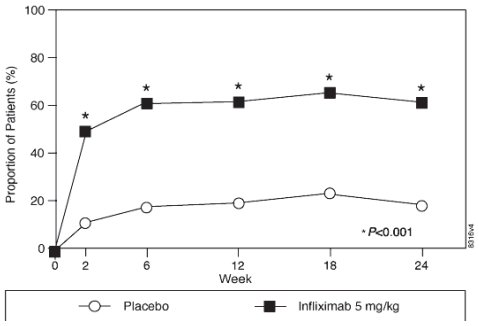


Figure 3 Proportion of patients achieving ASAS 20 response

At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE, compared to 9% and 4%, respectively, for patients receiving placebo (P<0.001, REMICADE vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of REMICADE-treated patients vs. 1% in placebo-treated patients (P<0.001).

Table 10 Components of ankylosing spondylitis disease activity

	Placebo (n=78)		REMICADE 5 mg/kg (n=201)		
	Baseline	24 Weeks	Baseline	24 Weeks	*P*-value
ASAS 20 response					
Criteria (Mean)					
Patient Global Assessment[a]	6.6	6.0	6.8	3.8	<0.001
Spinal pain[a]	7.3	6.5	7.6	4.0	<0.001
BASFI[b]	5.8	5.6	5.7	3.6	<0.001
Inflammation[c]	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP[d] (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test[e]	4.0	5.0	4.3	4.4	0.75
Chest expansion[e]	3.6	3.7	3.3	3.9	0.04
Tragus to wall[e]	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion[e]	10.6	11.0	11.4	12.9	0.03

[a] Measured on a VAS with 0="none" and 10="severe"
[b] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions
[c] Inflammation, average of last 2 questions on the 6-question BASDAI
[d] CRP normal range 0-1.0 mg/dL
[e] Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion: >6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm

The median improvement from baseline in the general health-related quality-of-life questionnaire SF-36 physical component summary score at Week 24 was 10.2 for the REMICADE group vs. 0.8 for the placebo group (P<0.001). There was no change in the SF-36 mental component summary score in either the REMICADE group or the placebo group.

Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled study of 70 patients with ankylosing spondylitis.

14.7 Psoriatic Arthritis

Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID therapy (≥5 swollen joints and ≥5 tender joints) with 1 or more of the following subtypes: arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients also had plaque psoriasis with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg REMICADE or placebo at Weeks 0, 2, 6, 14, and 22 (100 patients in each group). At Week 16, placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to REMICADE induction (early escape). At Week 24, all placebo-treated patients crossed over to REMICADE induction. Dosing continued for all patients through Week 46.

Clinical response

Treatment with REMICADE resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of REMICADE-treated patients achieving ACR 20 at Week 14, compared with 11% of placebo-treated patients ($P< 0.001$). The response was similar regardless of concomitant use of methotrexate. Improvement was observed as early as Week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving REMICADE compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

Compared to placebo, treatment with REMICADE resulted in improvements in the components of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 11). The clinical response was maintained through Week 54. Similar ACR responses were observed in an earlier randomized, placebo-controlled study of 104 psoriatic arthritis patients, and the responses were maintained through 98 weeks in an open-label extension phase.

Table 11 Components of ACR 20 and percentage of patients with 1 or more joints with dactylitis and percentage of patients with enthesopathy at baseline and Week 24

	Placebo		REMICADE 5 mg/kg[a]	
Patients Randomized	(n=100)		(n=100)	
	Baseline	Week 24	Baseline	Week 24
Parameter (medians)				
No. of Tender Joints[b]	24	20	20	6
No. of Swollen Joints[c]	12	9	12	3
Pain[d]	6.4	5.6	5.9	2.6
Physician's Global Assessment[d]	6.0	4.5	5.6	1.5
Patient's Global Assessment[d]	6.1	5.0	5.9	2.5
Disability Index (HAQ-DI)[e]	1.1	1.1	1.1	0.5
CRP (mg/dL)[f]	1.2	0.9	1.0	0.4
% Patients with 1 or more digits with dactylitis	41	33	40	15
% Patients with enthesopathy	35	36	42	22

[a] $P<0.001$ for percent change from baseline in all components of ACR 20 at Week 24, $P<0.05$ for % of patients with dactylitis, and $P=0.004$ for % of patients with enthesopathy at Week 24

[b] Scale 0-68

[c] Scale 0-66

[d] Visual Analog Scale (0=best, 10=worst)

[e] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

[f] Normal range 0-0.6 mg/dL

Improvement in Psoriasis Area and Severity Index (PASI) in psoriatic arthritis patients with baseline body surface area (BSA) ≥3% (n=87 placebo, n=83 REMICADE) was achieved at Week 14, regardless of concomitant methotrexate use, with 64% of REMICADE-treated patients achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients; improvement was observed in some patients as early as Week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving REMICADE compared to 1% and 0%, respectively, of patients receiving placebo. The PASI response was generally maintained through Week 54. *[See also Clinical Studies (14.8)].*

Radiographic response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints. The total modified vdH-S score is a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and feet. At Week 24, REMICADE-treated patients had less radiographic progression than placebo-treated patients (mean change of -0.70 vs. 0.82, $P<0.001$). REMICADE-treated patients also had less progression in their erosion scores (-0.56 vs 0.51) and JSN scores (-0.14 vs 0.31). The patients in the REMICADE group demonstrated continued inhibition of structural damage at Week 54. Most patients showed little or no change in the vdH-S score during this 12-month study (median change of 0 in both patients who initially received REMICADE or placebo). More patients in the placebo group (12%) had readily apparent radiographic progression compared with the REMICADE group (3%).

Physical function

Physical function status was assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. REMICADE-treated patients demonstrated significant improvement in physical function as assessed by HAQ-DI (median percent improvement in HAQ-DI score from baseline to Week 14 and 24 of 43% for REMICADE-treated patients vs 0% for placebo-treated patients).

During the placebo-controlled portion of the trial (24 weeks), 54% of REMICADE-treated patients achieved a clinically meaningful improvement in HAQ-DI (≥0.3 unit decrease) compared to 22% of placebo-treated patients. REMICADE-treated patients also demonstrated greater improvement in the SF-36 physical and mental component summary scores than placebo-treated patients. The responses were maintained for up to 2 years in an open-label extension study.

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14.8 Plaque Psoriasis

The safety and efficacy of REMICADE were assessed in 3 randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic, stable plaque psoriasis involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after Week 10 of study initiation.

Study I (EXPRESS) evaluated 378 patients who received placebo or REMICADE at a dose of 5 mg/kg at Weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks. At Week 24, the placebo group crossed over to REMICADE induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Patients originally randomized to REMICADE continued to receive REMICADE 5 mg/kg every 8 weeks through Week 46. Across all treatment groups, the median baseline PASI score was 21 and the baseline Static Physician Global Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe (2%). In addition, 75% of patients had a BSA >20%. Seventy-one percent of patients previously received systemic therapy, and 82% received phototherapy.

Study II (EXPRESS II) evaluated 835 patients who received placebo or REMICADE at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At Week 14, within each REMICADE dose group, patients were randomized to either scheduled (every 8 weeks) or as needed (PRN) maintenance treatment through Week 46. At Week 16, the placebo group crossed over to REMICADE induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Across all treatment groups, the median baseline PASI score was 18, and 63% of patients had a BSA >20%. Fifty-five percent of patients previously received systemic therapy, and 64% received a phototherapy.

Study III (SPIRIT) evaluated 249 patients who had previously received either psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or REMICADE at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At Week 26, patients with a sPGA score of moderate or worse (greater than or equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across all treatment groups, the median baseline PASI score was 19, and the baseline sPGA score ranged from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients had a BSA >20%. Of the enrolled patients, 114 (46%) received the Week 26 additional dose.

In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 by the PASI (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a score of "cleared" or "minimal" by the sPGA. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared" or "minimal," consisted of none or minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale over <5% of the plaque.

Study II also evaluated the proportion of patients who achieved a score of "clear" or "excellent" by the relative Physician's Global Assessment (rPGA). The rPGA is a 6-category scale ranging from "6 = worse" to "1 = clear" that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as "clear" or "excellent," consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

Table 12 Psoriasis studies I, II, and III, Week 10 percentage of patients who achieved PASI 75 and percentage who achieved treatment "success" with Physician's Global Assessment

	Placebo	REMICADE	
		3 mg/kg	5 mg/kg
Psoriasis Study I - patients randomized[a]	77	---	301
PASI 75	2 (3%)	---	242 (80%)*
sPGA	3 (4%)	---	242 (80%)*
Psoriasis Study II - patients randomized[a]	208	313	314
PASI 75	4 (2%)	220 (70%)*	237 (75%)*
rPGA	2 (1%)	217 (69%)*	234 (75%)*
Psoriasis Study III - patients randomized[b]	51	99	99
PASI 75	3 (6%)	71 (72%)*	87 (88%)*
sPGA	5 (10%)	71 (72%)*	89 (90%)*

* $P<0.001$ compared with placebo

[a] Patients with missing data at Week 10 were considered as nonresponders.

[b] Patients with missing data at Week 10 were imputed by last observation.

In Study I, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 85% of patients on 5 mg/kg REMICADE achieved a PASI 75 at Week 10 compared with 4% of patients on placebo.

In Study II, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 72% and 77% of patients on 3 mg/kg and 5 mg/kg REMICADE achieved a PASI 75 at Week 10 respectively compared with 1% on placebo. In Study II, among patients with more extensive psoriasis who had failed or were intolerant to phototherapy, 70% and 78% of patients on 3 mg/kg and 5 mg/kg REMICADE achieved a PASI 75 at Week 10 respectively, compared with 2% on placebo.

Maintenance of response was studied in a subset of 292 and 297 REMICADE-treated patients in the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at Week 10 and investigational site, patients in the active treatment groups were re-randomized to either a scheduled or as needed maintenance (PRN) therapy, beginning on Week 14.

The groups that received a maintenance dose every 8 weeks appear to have a greater percentage of patients maintaining a PASI 75 through week 50 as compared to patients who received the as-needed or PRN doses, and the best response was maintained with the 5 mg/kg every 8-week dose. These results are shown in Figure 4. At Week 46, when REMICADE serum concentrations were at trough level, in the every 8-week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in the 3 mg/kg every 8-week dose group compared to the 5 mg/kg group was associated with a lower percentage of patients with detectable trough serum infliximab levels. This may be related in part to higher antibody rates *[see Adverse Reactions (6.1)]*. In addition, in a subset of patients who had achieved a response at Week 10, maintenance of response appears to be greater in patients who received REMICADE every 8 weeks at the 5 mg/kg dose. Regardless of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a subpopulation of patients in each group over time. The results of Study I through Week 50 in the 5 mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

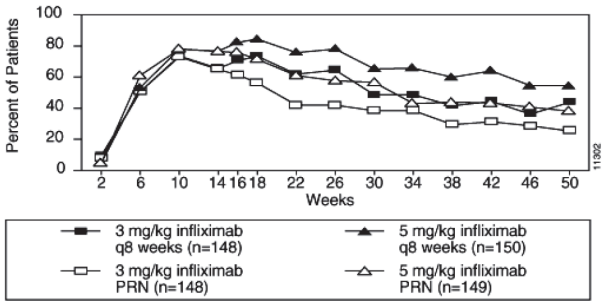


Figure 4 Proportion of patients achieving ≥75% improvement in PASI from baseline through Week 50; patients randomized at Week 14

Efficacy and safety of REMICADE treatment beyond 50 weeks have not been evaluated in patients with plaque psoriasis.

15 REFERENCES

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REMICADE® (infliximab)

16 HOW SUPPLIED/STORAGE AND HANDLING

Each REMICADE 20 mL vial is individually packaged in a carton. REMICADE is supplied in an accumulator carton containing 10 vials.

NDC 57894-030-01 100 mg vial

Each single dose vial contains 100 mg of infliximab for final reconstitution volume of 10 mL.

Storage and Stability

REMICADE must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Do not use REMICADE beyond the expiration date (Exp) located on the carton and the vial. This product contains no preservative.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

17.1 Patient Counseling

Patients or their caregivers should be advised of the potential benefits and risks of REMICADE. Physicians should instruct their patients to read the Medication Guide before starting REMICADE therapy and to reread it each time they receive an infusion. It is important that the patient's overall health be assessed at each treatment visit and that any questions resulting from the patient's or their caregiver's reading of the Medication Guide be discussed.

- Immunosuppression
  Inform patients that REMICADE may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctors if they develop any symptoms of an infection, including tuberculosis and reactivation of hepatitis B virus infections. Patients should be counseled about the risk of lymphoma and other malignancies while receiving REMICADE.
- Other Medical Conditions
  Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report any symptoms of a cytopenia such as bruising, bleeding or persistent fever.

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Remicade® INFLIXIMAB (Rem-eh-kaid)

MEDICATION GUIDE
REMICADE® (Rem-eh-kaid)
(infliximab)

Read the Medication Guide that comes with REMICADE before you receive the first treatment, and before each time you get a treatment of REMICADE. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about REMICADE?

REMICADE may cause serious side effects, including:

1. Risk of infection

REMICADE is a medicine that affects your immune system. REMICADE can lower the ability of your immune system to fight infections. Serious infections have happened in patients receiving REMICADE. These infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some patients have died from these infections.

- Your doctor should test you for TB before starting REMICADE.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with REMICADE.

Before starting REMICADE, tell your doctor if you:

- think you have an infection. You should not start taking REMICADE if you have any kind of infection.
- are being treated for an infection.
- have signs of an infection, such as a fever, cough, flu-like symptoms.
- have any open cuts or sores on your body.
- get a lot of infections or have infections that keep coming back.
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may develop or become more severe if you take REMICADE. If you do not know if you have lived in an area where histoplasmosis, coccidioidomycosis, or blastomycosis is common, ask your doctor.
- have or have had hepatitis B.
- use the medicines KINERET (anakinra), ORENCIA (abatacept), ACTEMRA (tocilizumab), or other medicines called biologics used to treat the same conditions as REMICADE.

After starting REMICADE, if you have an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have open cuts or sores on your body, call your doctor right away. REMICADE can make you more likely to get infections or make any infection that you have worse.

2. Risk of Cancer

- There have been cases of unusual cancers in children and teenage patients using TNF-blocking agents.
- For children and adults taking TNF-blocker medicines, including REMICADE, the chances of getting lymphoma or other cancers may increase.
- Some people receiving TNF-blockers, including REMICADE, developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with a TNF-blocker and another medicine called azathioprine or 6-mercaptopurine.
- People who have been treated for rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis for a long time may be more likely to develop lymphoma. This is especially true for people with very active disease.
- Some people treated with REMICADE have developed certain kinds of skin cancer. If any changes in the appearance of your skin or growths on your skin occur during or after your treatment with REMICADE, tell your doctor.
- Patients with COPD (a specific type of lung disease) may have an increased risk for getting cancer while being treated with REMICADE.
- Tell your doctor if you have ever had any type of cancer. Discuss with your doctor any need to adjust medicines you may be taking.

See the section **"What are the possible side effects of REMICADE?"** below for more information.

What is REMICADE?

REMICADE is a prescription medicine that is approved for patients with:

- Rheumatoid Arthritis - adults with moderately to severely active rheumatoid arthritis, along with the medicine methotrexate
- Crohn's Disease - children 6 years and older and adults with Crohn's disease who have not responded well to other medicines
- Ankylosing Spondylitis
- Psoriatic Arthritis
- Plaque Psoriasis - adult patients with plaque psoriasis that is chronic (doesn't go away) severe, extensive, and/or disabling.
- Ulcerative Colitis - children 6 years and older and adults with moderately to severely active ulcerative colitis who have not responded well to other medicines.

REMICADE blocks the action of a protein in your body called tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is made by your body's immune system. People with certain diseases have too much TNF-alpha that can cause the immune system to attack normal healthy parts of the body. REMICADE can block the damage caused by too much TNF-alpha.

Who should not receive REMICADE?

You should not receive REMICADE if you have:

- heart failure, unless your doctor has examined you and decided that you are able to take REMICADE. Talk to your doctor about your heart failure.
- had an allergic reaction to REMICADE, or any of the other ingredients in REMICADE. See the end of this Medication Guide for a complete list of ingredients in REMICADE.

What should I tell my doctor before starting treatment with REMICADE?

Your doctor will assess your health before each treatment.

Tell your doctor about all of your medical conditions, including if you:

- have an infection (see **"What is the most important information I should know about REMICADE?"**).
- have other liver problems including liver failure.
- have heart failure or other heart conditions. If you have heart failure, it may get worse while you take REMICADE.
- have or have had any type of cancer.

- have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine to make your skin sensitive to light) for psoriasis. You may have a higher chance of getting skin cancer while receiving REMICADE.
- have COPD (Chronic Obstructive Pulmonary Disease), a specific type of lung disease. Patients with COPD may have an increased risk of getting cancer while taking REMICADE.
- have or have had a condition that affects your nervous system such as
  - multiple sclerosis, or Guillain-Barré syndrome, or
  - if you experience any numbness or tingling, or
  - if you have had a seizure.
- have recently received or are scheduled to receive a vaccine. **Adults and children taking REMICADE should not receive live vaccines or treatment with a weakened bacteria** (such as BCG for bladder cancer). Children should have all of their vaccines brought up to date before starting treatment with REMICADE.
- are pregnant or planning to become pregnant. It is not known if REMICADE harms your unborn baby. REMICADE should be given to a pregnant woman only if clearly needed. Talk to your doctor about stopping REMICADE if you are pregnant or planning to become pregnant.
- are breast-feeding or planning to breast-feed. It is not known whether REMICADE passes into your breast milk. Talk to your doctor about the best way to feed your baby while taking REMICADE. You should not breast-feed while taking REMICADE.

If you have a baby and you were using REMICADE during your pregnancy, it is important to tell your baby's doctor and other health care professionals about your REMICADE use so they can decide when your baby should receive any vaccine. Certain vaccinations may cause infections.

If you received REMICADE while you were pregnant, your baby may be at higher risk for getting an infection for at least six months after the last dose of REMICADE you received during your pregnancy.

How should I receive REMICADE?

- You will be given REMICADE through a needle placed in a vein (IV or intravenous infusion) in your arm.
- Your doctor may decide to give you medicine before starting the REMICADE infusion to prevent or lessen side effects.
- Only a healthcare professional should prepare the medicine and administer it to you.
- REMICADE will be given to you over a period of about 2 hours.
- If you have side effects from REMICADE, the infusion may need to be adjusted or stopped. In addition, your healthcare professional may decide to treat your symptoms.
- A healthcare professional will monitor you during the REMICADE infusion and for a period of time afterward for side effects. Your doctor may do certain tests while you are taking REMICADE to monitor you for side effects and to see how well you respond to the treatment.
- Your doctor will determine the right dose of REMICADE for you and how often you should receive it. Make sure to discuss with your doctor when you will receive infusions and to come in for all your infusions and follow-up appointments.

What should I avoid while receiving REMICADE?

Do not take REMICADE together with medications such as KINERET (anakinra), ORENCIA (abatacept), ACTEMRA (tocilizumab), or other medicines called biologics that are used to treat the same conditions as REMICADE.

REMICADE® (infliximab)

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. These include any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis.

Know the medicines you take. Keep a list of your medicines and show them to your doctor and pharmacist when you get a new medicine.

What are the possible side effects of REMICADE?

REMICADE can cause serious side effects, including:

See "**What is the most important information I should know about REMICADE?"**.

Serious Infections

- Some patients, especially those 65 years and older have had serious infections while receiving REMICADE. These serious infections include TB and infections caused by viruses, fungi, or bacteria that have spread throughout the body. Some patients die from these infections. If you get an infection while receiving treatment with REMICADE your doctor will treat your infection and may need to stop your REMICADE treatment.
- Tell your doctor right away if you have any of the following signs of an infection while taking or after taking REMICADE:
  - a fever
  - feel very tired
  - have a cough
  - have flu-like symptoms
  - warm, red, or painful skin
- Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with REMICADE and during treatment with REMICADE.
- Even if your TB test is negative, your doctor should carefully monitor you for TB infections while you are taking REMICADE. Patients who had a **negative** TB skin test before receiving REMICADE have developed active TB.
- If you are a chronic carrier of the hepatitis B virus, the virus can become active while you are being treated with REMICADE. In some cases, patients have died as a result of hepatitis B virus being reactivated. Your doctor should do a blood test for hepatitis B virus before you start treatment with REMICADE and occasionally while you are being treated. Tell your doctor if you have any of the following symptoms:
  - feel unwell
  - poor appetite
  - tiredness (fatigue)
  - fever, skin rash and/or joint pain

Heart Failure

If you have a heart problem called congestive heart failure, your doctor should check you closely while you are taking REMICADE. Your congestive heart failure may get worse while you are taking REMICADE. Be sure to tell your doctor of any new or worse symptoms including:

- shortness of breath
- swelling of ankles or feet
- sudden weight gain

Treatment with REMICADE may need to be stopped if you get new or worse congestive heart failure.

Liver Injury

In rare cases, some patients taking REMICADE have developed serious liver problems. Tell your doctor if you have

- jaundice (skin and eyes turning yellow)
- dark brown-colored urine
- pain on the right side of your stomach area (right-sided abdominal pain)
- fever
- extreme tiredness (severe fatigue)

Blood Problems

In some patients taking REMICADE, the body may not make enough of the blood cells that help fight infections or help stop bleeding. Tell your doctor if you

- have a fever that does not go away
- bruise or bleed very easily
- look very pale

Nervous System Disorders

In rare cases, patients taking REMICADE have developed problems with their nervous system. Tell your doctor if you have

- changes in your vision
- weakness in your arms and/or legs
- numbness or tingling in any part of your body
- seizures

Allergic Reactions

Some patients have had allergic reactions to REMICADE. Some of these reactions were severe. These reactions can happen while you are getting your REMICADE treatment or shortly afterward. Your doctor may need to stop or pause your treatment with REMICADE and may give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:

- hives (red, raised, itchy patches of skin)
- difficulty breathing
- chest pain
- high or low blood pressure
- fever
- chills

Some patients treated with REMICADE have had delayed allergic reactions. The delayed reactions occurred 3 to 12 days after receiving treatment with REMICADE. Tell your doctor right away if you have any of these signs of delayed allergic reaction to REMICADE:

- fever
- rash
- headache
- sore throat
- muscle or joint pain
- swelling of the face and hands
- difficulty swallowing

Lupus-like Syndrome

Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any of the following symptoms, your doctor may decide to stop your treatment with REMICADE.

- chest discomfort or pain that does not go away
- shortness of breath
- joint pain
- rash on the cheeks or arms that gets worse in the sun

Psoriasis

Some people using REMICADE had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps on the skin that are filled with pus. Your doctor may decide to stop your treatment with REMICADE.

The most common side effects of REMICADE include:

- respiratory infections, such as sinus infections and sore throat
- headache
- coughing
- stomach pain

Infusion reactions can happen up to 2 hours after your infusion of REMICADE. Symptoms of infusion reactions may include:

- fever
- chills
- chest pain
- low blood pressure or high blood pressure
- shortness of breath
- rash
- itching

Children who took REMICADE in studies for Crohn's disease showed some differences in side effects compared with adults who took REMICADE for Crohn's disease. The side effects that happened more in children were: anemia (low red blood cells), leukopenia (low white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils, the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions of the breathing tract. Among patients who took REMICADE for ulcerative colitis in clinical studies, more children had infections as compared with adults.

Tell your doctor about any side effect that bothers you or does not go away.

These are not all of the side effects with REMICADE. Ask your doctor or pharmacist for more information.

General information about REMICADE

Medicines are sometimes prescribed for purposes that are not mentioned in Medication Guides or patient information sheets. Do not use REMICADE for a condition for which it was not prescribed.

This information sheet summarizes the most important information about REMICADE. You can ask your doctor or pharmacist for information about REMICADE that is written for health professionals.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

For more information go to www.remicade.com, or call 1-800-JANSSEN (1-800-526-7736).

What are the ingredients in REMICADE?

The active ingredient is Infliximab.

The inactive ingredients in REMICADE include: sucrose, polysorbate 80, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate dihydrate. No preservatives are present.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044 U.S. License No. 1864

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This Medication Guide has been approved by the U.S. Food and Drug Administration

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https://web.archive.org/web/20161013234751/http://www.rxabbvie.com/pdf/humira.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HUMIRA safely and effectively. See full prescribing information for HUMIRA.

HUMIRA (adalimumab) injection, for subcutaneous use
Initial U.S. Approval: 2002

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):
- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

MALIGNANCY (5.2):
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.**
- **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.**

RECENT MAJOR CHANGES

Indications and Usage, Hidradenitis Suppurativa (1.9)	9/2015
Indications and Usage, Uveitis (1.10)	6/2016
Dosage and Administration, Plaque Psoriasis and Uveitis (2.6)	6/2016
Dosage and Administration, Hidradenitis Suppurativa (2.7)	9/2015
Dosage and Administration, General Considerations for Administration (2.9)	11/2015
Warnings and Precautions, Malignancies (5.2)	6/2016
Warnings and Precautions, Neurologic Reactions (5.5)	6/2016
Warnings and Precautions, Immunizations (5.10)	6/2016

INDICATIONS AND USAGE

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:
- **Rheumatoid Arthritis (RA) (1.1):** Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA) (1.2):** Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.
- **Psoriatic Arthritis (PsA) (1.3):** Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS) (1.4):** Reducing signs and symptoms in adult patients with active AS.
- **Adult Crohn's Disease (CD) (1.5):** Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
- **Pediatric Crohn's Disease (1.6):** Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.
- **Ulcerative Colitis (UC) (1.7):** Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps) (1.8):** The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
- **Hidradenitis Suppurativa (HS) (1.9):** The treatment of moderate to severe hidradenitis suppurativa.
- **Uveitis (UV) (1.10):** The treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

DOSAGE AND ADMINISTRATION

- Administered by subcutaneous injection (2)

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):
- 40 mg every other week.
  - Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.

Juvenile Idiopathic Arthritis (2.2):
- *10 kg (22 lbs) to <15 kg (33 lbs):* 10 mg every other week
- *15 kg (33 lbs) to < 30 kg (66 lbs):* 20 mg every other week
- *≥ 30 kg (66 lbs):* 40 mg every other week

Adult Crohn's Disease and Ulcerative Colitis (2.3, 2.5):
- Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days)
- Second dose two weeks later (Day 15): 80 mg
  - Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.
- For patients with Ulcerative Colitis only: Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy.

Pediatric Crohn's Disease (2.4):
- ***17 kg (37 lbs) to < 40 kg (88 lbs):***
  - Initial dose (Day 1): 80 mg (two 40 mg injections in one day)
  - Second dose two weeks later (Day 15): 40 mg
    - Two weeks later (Day 29): Begin a maintenance dose of 20 mg every other week.
- ***≥ 40 kg (88 lbs):***
  - Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days)
  - Second dose two weeks later (Day 15): 80 mg (two 40 mg injections in one day)
    - Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.

Plaque Psoriasis or Uveitis (2.6):
- 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

Hidradenitis Suppurativa (2.7):
- Initial dose (Day 1): 160 mg (given as four 40 mg injections on Day 1 or as two 40 mg injections per day on Days 1 and 2)
- Second dose two weeks later (Day 15): 80 mg (two 40 mg injections in one day)
- Third (Day 29) and subsequent doses: 40 mg every week.

DOSAGE FORMS AND STRENGTHS

- Injection: 40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- Injection: 40 mg/0.4 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe (3)
- Injection: 40 mg/0.4 mL in a single-use prefilled glass syringe (3)
- Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe (3)
- Injection: 10 mg/0.2 mL in a single-use prefilled glass syringe (3)
- Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use only (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- *Serious infections:* Do not start HUMIRA during an active infection. If an infection develops, monitor carefully, and stop HUMIRA if infection becomes serious (5.1)
- *Invasive fungal infections:* For patients who develop a systemic illness on HUMIRA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic (5.1)
- *Malignancies:* Incidence of malignancies was greater in HUMIRA-treated patients than in controls (5.2)
- *Anaphylaxis or serious allergic reactions* may occur (5.3)

- *Hepatitis B virus reactivation:* Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop HUMIRA and begin anti-viral therapy (5.4)
- *Demyelinating disease:* Exacerbation or new onset, may occur (5.5)
- *Cytopenias, pancytopenia:* Advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA (5.6)
- *Heart failure:* Worsening or new onset, may occur (5.8)
- *Lupus-like syndrome:* Stop HUMIRA if syndrome develops (5.9)

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions (incidence >10%): infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- **DRUG INTERACTIONS** ----------

- *Abatacept:* Increased risk of serious infection (5.1, 5.11, 7.2)
- *Anakinra:* Increased risk of serious infection (5.1, 5.7, 7.2)
- *Live vaccines:* Avoid use with HUMIRA (5.10, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2016

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions (5.2)]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in

combination with these other immunosuppressants *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

1.2 Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

1.3 Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

1.4 Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

1.5 Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

1.6 Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

1.7 Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The

effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers *[see Clinical Studies (14.7)]*.

1.8 Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions (5)]*.

1.9 Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

1.10 Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

2 DOSAGE AND ADMINISTRATION

HUMIRA is administered by subcutaneous injection.

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

The recommended dose of HUMIRA for adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) is 40 mg administered every other week. Methotrexate (MTX), other non-biologic DMARDS, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with HUMIRA. In the treatment of RA, some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

2.2 Juvenile Idiopathic Arthritis

The recommended dose of HUMIRA for patients 2 years of age and older with polyarticular juvenile idiopathic arthritis (JIA) is based on weight as shown below. MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with HUMIRA.

Patients (2 years of age and older)	**Dose**
10 kg (22 lbs) to <15 kg (33 lbs)	10 mg every other week (10 mg Prefilled Syringe)
15 kg (33 lbs) to <30 kg (66 lbs)	20 mg every other week (20 mg Prefilled Syringe)
≥30 kg (66 lbs)	40 mg every other week (HUMIRA Pen or 40 mg Prefilled Syringe)

HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

2.3 Adult Crohn's Disease

The recommended HUMIRA dose regimen for adult patients with Crohn's disease (CD) is 160 mg initially on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine, 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* or MTX may be continued during treatment with HUMIRA if necessary. The use of HUMIRA in CD beyond one year has not been evaluated in controlled clinical studies.

2.4 Pediatric Crohn's Disease

The recommended HUMIRA dose regimen for pediatric patients 6 years of age and older with Crohn's disease (CD) is based on body weight as shown below:

Pediatric Patients	Induction Dose	Maintenance Dose Starting at Week 4 (Day 29)
17 kg (37 lbs) to < 40 kg (88 lbs)	• 80 mg on Day 1 (administered as two 40 mg injections in one day); and • 40 mg two weeks later (on Day 15)	• 20 mg every other week
≥ 40 kg (88 lbs)	• 160 mg on Day 1 (administered as four injections in one day or as two 40 mg injections per day for two consecutive days); and • 80 mg two weeks later (on Day 15) (administered as two 40 mg injections in one day)	• 40 mg every other week

2.5 Ulcerative Colitis

The recommended HUMIRA dose regimen for adult patients with ulcerative colitis (UC) is 160 mg initially on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) continue with a dose of 40 mg every other week.

Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine and 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* may be continued during treatment with HUMIRA if necessary.

2.6 Plaque Psoriasis or Uveitis

The recommended dose of HUMIRA for adult patients with plaque psoriasis (Ps) or Uveitis (UV) is an initial dose of 80 mg, followed by 40 mg given every other week starting one week

after the initial dose. The use of HUMIRA in moderate to severe chronic Ps beyond one year has not been evaluated in controlled clinical studies.

2.7 Hidradenitis Suppurativa

The recommended dose of HUMIRA for adult patients with hidradenitis suppurativa (HS) is 160 mg (given as four 40 mg injections on Day 1 or as two 40 mg injections per day on Days 1 and 2), followed by 80 mg two weeks later (Day 15). Begin 40 mg weekly dosing two weeks later (Day 29).

2.8 Monitoring to Assess Safety

Prior to initiating HUMIRA and periodically during therapy, evaluate patients for active tuberculosis and test for latent infection *[see Warnings and Precautions (5.1)]*.

2.9 General Considerations for Administration

HUMIRA is intended for use under the guidance and supervision of a physician. A patient may self-inject HUMIRA or a caregiver may inject HUMIRA using either the HUMIRA Pen or prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

You may leave HUMIRA at room temperature for about 15 to 30 minutes before injecting. Do not remove the cap or cover while allowing it to reach room temperature. Carefully inspect the solution in the HUMIRA Pen, prefilled syringe, or single-use institutional use vial for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, do not use the product. HUMIRA does not contain preservatives; therefore, discard unused portions of drug remaining from the syringe. NOTE: Instruct patients sensitive to latex not to handle the gray needle cover of the 27 gauge HUMIRA Pen and prefilled syringe because it contains natural rubber latex *[see How Supplied/Storage and Handling (16) for specific information]*.

Instruct patients using the HUMIRA Pen or prefilled syringe to inject the full amount in the syringe, according to the directions provided in the Instructions for Use *[see Instructions for Use]*.

Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

The HUMIRA single-use institutional use vial is for administration within an institutional setting only, such as a hospital, physician's office or clinic. Withdraw the dose using a sterile needle and syringe and administer promptly by a healthcare provider within an institutional setting. Only administer one dose per vial. The vial does not contain preservatives; therefore, discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

- **Pen**
  Injection: 40 mg/0.8 mL of HUMIRA is provided by a single-use pen (HUMIRA Pen), containing a 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle and a gray

needle cover.
Injection: 40 mg/0.4 mL of HUMIRA is provided by a single-use pen (HUMIRA Pen), containing a 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle and a black needle cover.

- **Prefilled Syringe**
  Injection: 40 mg/0.8 mL of HUMIRA is provided by a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle and a gray needle cover.
  Injection: 40 mg/0.4 mL of HUMIRA is provided by a single-use, 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle and a black needle cover.
  Injection: 20 mg/0.4 mL of HUMIRA is provided by a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle and a gray needle cover.
  Injection: 10 mg/0.2 mL of HUMIRA is provided by a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle and a gray needle cover.
- **Single-Use Institutional Use Vial**
  Injection: 40 mg/0.8 mL of HUMIRA is provided by a single-use, glass vial for institutional use only.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions (5.7, 5.11) and Drug Interactions (7.2)]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;

- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being

performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

5.2 Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps), hidradenitis suppurativa (HS) and uveitis (UV), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1]

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated

patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

5.3 Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

5.4 Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

5.5 Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

5.6 Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

5.7 Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions (7.2)]*.

5.8 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

5.9 Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions (6.1)]*.

5.10 Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations (8.1, 8.4)]*.

5.11 Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions (7.2)]*.

6 ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions (5.1)]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions (5.1)]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the

recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL

(approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%

Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%
* Laboratory test abnormalities were reported as adverse reactions in European trials ** Does not include injection site erythema, itching, hemorrhage, pain or swelling		

Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies

Other infrequent serious adverse reactions that do not appear in the Warnings and Precautions or Adverse Reaction sections that occurred at an incidence of less than 5% in HUMIRA-treated patients in RA studies were:

Body As A Whole: Pain in extremity, pelvic pain, surgery, thorax pain

Cardiovascular System: Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, polycythemia

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma

Nervous System: Confusion, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions (5), Adverse Reactions (6)]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

7 DRUG INTERACTIONS

7.1 Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do

not suggest the need for dose adjustment of either HUMIRA or MTX *[see Clinical Pharmacology (12.3)]*.

7.2 Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions (5.7 and 5.11)]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

7.3 Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions (5.10)]*.

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [*see Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations (8.4)]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of

adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations (8.1)]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions (5.2)]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies (14.2)]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions (6.1)]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions (6.1)]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies (14.6)]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

8.5 Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was

higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

10 OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). HUMIRA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen), as a single-use, 1 mL prefilled glass syringe, or as a single-use institutional use vial. Enclosed within the pen is a single-use, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2.

Each 40 mg/0.4 mL prefilled syringe or prefilled pen delivers 0.4 mL (40 mg) of drug product. Each 0.4 mL of HUMIRA contains adalimumab 40 mg, mannitol 16.8 mg, polysorbate 80 0.4 mg, and Water for Injection, USP.

Each 40 mg/0.8 mL prefilled syringe, prefilled pen, or single-use institutional use vial delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains adalimumab 40 mg, citric acid monohydrate 1.04 mg, dibasic sodium phosphate dihydrate 1.22 mg, mannitol 9.6 mg, monobasic sodium phosphate dihydrate 0.69 mg, polysorbate 80 0.8 mg, sodium chloride 4.93 mg, sodium citrate 0.24 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

Each 20 mg/0.4 mL prefilled syringe delivers 0.4 mL (20 mg) of drug product. Each 0.4 mL of HUMIRA contains adalimumab 20 mg, citric acid monohydrate 0.52 mg, dibasic sodium phosphate dihydrate 0.61 mg, mannitol 4.8 mg, monobasic sodium phosphate dihydrate 0.34 mg, polysorbate 80 0.4 mg, sodium chloride 2.47 mg, sodium citrate 0.12 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

Each 10 mg/0.2 mL prefilled syringe delivers 0.2 mL (10 mg) of drug product. Each 0.2 mL of HUMIRA contains adalimumab 10 mg, citric acid monohydrate 0.26 mg, dibasic sodium phosphate dihydrate 0.31 mg, mannitol 2.4 mg, monobasic sodium phosphate dihydrate 0.17 mg, polysorbate 80 0.2 mg, sodium chloride 1.23 mg, sodium citrate 0.06 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In Ps, treatment with HUMIRA may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

12.2 Pharmacodynamics

After treatment with HUMIRA, a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease, ulcerative colitis and hidradenitis suppurativa. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

12.3 Pharmacokinetics

The maximum serum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were 4.7 ± 1.6 µg/mL and 131 ± 56 hours respectively, following a single 40 mg subcutaneous administration of HUMIRA to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

The single dose pharmacokinetics of adalimumab in RA patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

In RA patients receiving 40 mg HUMIRA every other week, adalimumab mean steady-state trough concentrations of approximately 5 µg/mL and 8 to 9 µg/mL, were observed without and with methotrexate (MTX), respectively. MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA. Mean serum adalimumab trough levels at steady state increased approximately proportionally with dose

following 20, 40, and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Adalimumab mean steady-state trough concentrations were slightly higher in psoriatic arthritis patients treated with 40 mg HUMIRA every other week (6 to 10 µg/mL and 8.5 to 12 µg/mL, without and with MTX, respectively) compared to the concentrations in RA patients treated with the same dose.

The pharmacokinetics of adalimumab in patients with AS were similar to those in patients with RA.

In patients with CD, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 µg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 µg/mL were observed at Week 24 and Week 56 in CD patients after receiving a maintenance dose of 40 mg HUMIRA every other week.

In patients with UC, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 µg/mL at Week 2 and Week 4. Mean steady-state trough level of approximately 8 µg/mL was observed at Week 52 in UC patients after receiving a dose of 40 mg HUMIRA every other week, and approximately 15 µg/mL at Week 52 in UC patients who increased to a dose of 40 mg HUMIRA every week.

In patients with Ps, the mean steady-state trough concentration was approximately 5 to 6 µg/mL during HUMIRA 40 mg every other week monotherapy treatment.

In subjects with HS, a dose of 160 mg HUMIRA on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 µg/mL at Week 2 and Week 4. The mean steady-state trough concentrations at Week 12 through Week 36 were approximately 7 to 11 µg/mL during HUMIRA 40 mg every week treatment.

In patients with UV, the mean steady concentration was approximately 8 to 10 µg/mL during HUMIRA 40 mg every other week treatment.

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to >75 years.

Minor increases in apparent clearance were also predicted in RA patients receiving doses lower than the recommended dose and in RA patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

In Study JIA-I for patients with polyarticular JIA who were 4 to 17 years of age, the mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg receiving 20

mg HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.8 μg/mL and 10.9 μg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥30 kg receiving 40 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.6 μg/mL and 8.1 μg/mL, respectively. In Study JIA-II for patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, the mean steady-state trough serum adalimumab concentrations for patients receiving HUMIRA subcutaneously every other week as monotherapy or with concomitant MTX were 6.0 μg/mL and 7.9 μg/mL, respectively.

In pediatric subjects with CD weighing ≥ 40 kg, the mean ±SD serum adalimumab concentrations were 15.7±6.5 mcg/mL at Week 4 following subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 and the mean ±SD steady-state trough serum adalimumab concentrations were 10.5±6.0 mcg/mL at Week 52 following subcutaneous doses of 40 mg every other week. In pediatric subjects with CD weighing < 40 kg, the mean ±SD serum adalimumab concentrations were 10.6±6.1 mcg/mL at Week 4 following subcutaneous doses of 80 mg at Week 0 and 40 mg at Week 2 and the mean ±SD steady-state trough serum adalimumab concentrations were 6.9±3.6 mcg/mL at Week 52 following subcutaneous doses of 20 mg every other week.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of HUMIRA were assessed in five randomized, double-blind studies in patients ≥18 years of age with active rheumatoid arthritis (RA) diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. HUMIRA was administered subcutaneously in combination with methotrexate (MTX) (12.5 to 25 mg, Studies RA-I, RA-III and RA-V) or as monotherapy (Studies RA-II and RA-V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study RA-IV).

Study RA-I evaluated 271 patients who had failed therapy with at least one but no more than four DMARDs and had inadequate response to MTX. Doses of 20, 40 or 80 mg of HUMIRA or placebo were given every other week for 24 weeks.

Study RA-II evaluated 544 patients who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given as monotherapy every other week or weekly for 26 weeks.

Study RA-III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study RA-III had an additional primary endpoint at

52 weeks of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to 5 years.

Study RA-IV assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Study RA-V evaluated 799 patients with moderately to severely active RA of less than 3 years duration who were ≥18 years old and MTX naïve. Patients were randomized to receive either MTX (optimized to 20 mg/week by week 8), HUMIRA 40 mg every other week or HUMIRA/MTX combination therapy for 104 weeks. Patients were evaluated for signs and symptoms, and for radiographic progression of joint damage. The median disease duration among patients enrolled in the study was 5 months. The median MTX dose achieved was 20 mg.

Clinical Response

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies RA-II and III are shown in Table 2.

Table 2. ACR Responses in Studies RA-II and RA-III (Percent of Patients)

	Study RA-II Monotherapy (26 weeks)			**Study RA-III Methotrexate Combination (24 and 52 weeks)**	
Response	Placebo	HUMIRA	HUMIRA	Placebo/MTX	HUMIRA/MTX
		40 mg every	40 mg weekly		40 mg every
		other week			other week
	N=110	N=113	N=103	N=200	N=207
ACR20					
Month 6	19%	46%*	53%*	30%	63%*
Month 12	NA	NA	NA	24%	59%*
ACR50					
Month 6	8%	22%*	35%*	10%	39%*
Month 12	NA	NA	NA	10%	42%*
ACR70					
Month 6	2%	12%*	18%*	3%	21%*
Month 12	NA	NA	NA	5%	23%*
* $p<0.01$, HUMIRA *vs.* placebo					

The results of Study RA-I were similar to Study RA-III; patients receiving HUMIRA 40 mg every other week in Study RA-I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months ($p<0.01$).

The results of the components of the ACR response criteria for Studies RA-II and RA-III are shown in Table 3. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study RA-III, 20% of HUMIRA patients receiving 40 mg every other week (EOW) achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to 5 years with continuous HUMIRA treatment in the open-label portion of Study RA-III.

Table 3. Components of ACR Response in Studies RA-II and RA-III

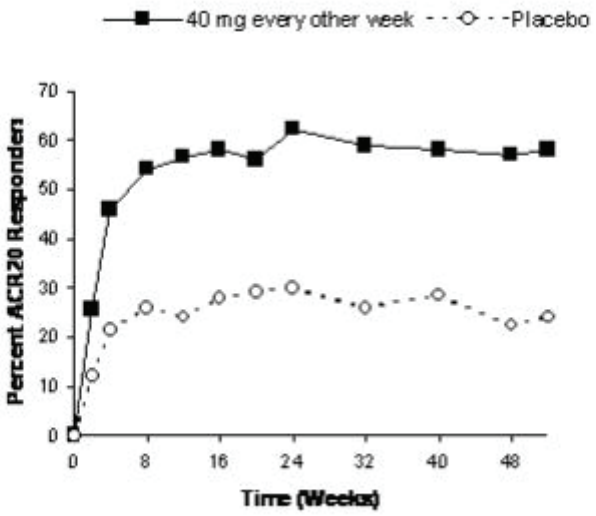
	Study RA-II				**Study RA-III**			
Parameter (median)	**Placebo N=110**		**HUMIRA[a] N=113**		**Placebo/MTX N=200**		**HUMIRA[a]/MTX N=207**	
	Baseline	**Wk 26**	**Baseline**	**Wk 26**	**Baseline**	**Wk 24**	**Baseline**	**Wk 24**
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0-66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

[a] 40 mg HUMIRA administered every other week
[b] Visual analogue scale; 0 = best, 10 = worst
[c] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity
* $p<0.001$, HUMIRA *vs.* placebo, based on mean change from baseline

The time course of ACR 20 response for Study RA-III is shown in Figure 1.

In Study RA-III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study RA-I and Study RA-II were similar.

Figure 1. Study RA-III ACR 20 Responses over 52 Weeks



In Study RA-IV, 53% of patients treated with HUMIRA 40 mg every other week plus standard of care had an ACR 20 response at week 24 compared to 35% on placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of HUMIRA (adalimumab) and other DMARDs were observed.

In Study RA-V with MTX naïve patients with recent onset RA, the combination treatment with HUMIRA plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or HUMIRA monotherapy at Week 52 and responses were sustained at Week 104 (see Table 4).

Table 4. ACR Response in Study RA-V (Percent of Patients)

Response	**MTX[b] N=257**	**HUMIRA[c] N=274**	**HUMIRA/MTX N=268**
ACR20			
Week 52	63%	54%	73%
Week 104	56%	49%	69%
ACR50			
Week 52	46%	41%	62%
Week 104	43%	37%	59%
ACR70			
Week 52	27%	26%	46%
Week 104	28%	28%	47%
Major Clinical Response [a]	28%	25%	49%

[a] Major clinical response is defined as achieving an ACR70 response for a continuous six month period
[b] $p<0.05$, HUMIRA/MTX *vs.* MTX for ACR 20
$p<0.001$, HUMIRA/MTX *vs.* MTX for ACR 50 and 70, and Major Clinical Response
[c] $p<0.001$, HUMIRA/MTX *vs.* HUMIRA

At Week 52, all individual components of the ACR response criteria for Study RA-V improved in the HUMIRA/MTX group and improvements were maintained to Week 104.

Radiographic Response

In Study RA-III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 5. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 5. Radiographic Mean Changes Over 12 Months in Study RA-III

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX-HUMIRA/MTX (95% Confidence Interval*)	P-value**
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002
*95% confidence intervals for the differences in change scores between MTX and HUMIRA. **Based on rank analysis				

In the open-label extension of Study RA-III, 77% of the original patients treated with any dose of HUMIRA were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS. Fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less. Fifty-five percent (55%) of patients originally treated with 40 mg HUMIRA every other week have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage with 50% showing no progression of structural damage defined by a change in the TSS of zero or less.

In Study RA-V, structural joint damage was assessed as in Study RA-III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 6).

Table 6. Radiographic Mean Change* in Study RA-V

		MTX[a] N=257	**HUMIRA[a,b] N=274**	**HUMIRA/MTX N=268**
52 Weeks	Total Sharp score	5.7 (4.2, 7.3)	3.0 (1.7, 4.3)	1.3 (0.5, 2.1)
	Erosion score	3.7 (2.7, 4.8)	1.7 (1.0, 2.4)	0.8 (0.4, 1.2)
	JSN score	2.0 (1.2, 2.8)	1.3 (0.5, 2.1)	0.5 (0.0, 1.0)
104 Weeks	Total Sharp score	10.4 (7.7, 13.2)	5.5 (3.6, 7.4)	1.9 (0.9, 2.9)
	Erosion score	6.4 (4.6, 8.2)	3.0 (2.0, 4.0)	1.0 (0.4, 1.6)
	JSN score	4.1 (2.7, 5.4)	2.6 (1.5, 3.7)	0.9 (0.3, 1.5)
* mean (95% confidence interval)				

[a] p<0.001, HUMIRA/MTX *vs.* MTX at 52 and 104 weeks and for HUMIRA/MTX *vs.* HUMIRA at 104 weeks
[b] p<0.01, for HUMIRA/MTX *vs.* HUMIRA at 52 weeks

Physical Function Response

In studies RA-I through IV, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ-DI) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by The Short Form Health Survey (SF 36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

In Study RA-III, the mean (95% CI) improvement in HAQ-DI from baseline at week 52 was 0.60 (0.55, 0.65) for the HUMIRA patients and 0.25 (0.17, 0.33) for placebo/MTX (p<0.001) patients. Sixty-three percent of HUMIRA-treated patients achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study. Eighty-two percent of these patients maintained that improvement through week 104 and a similar proportion of patients maintained this response through week 260 (5 years) of open-label treatment. Mean improvement in the SF-36 was maintained through the end of measurement at week 156 (3 years).

In Study RA-V, the HAQ-DI and the physical component of the SF-36 showed greater improvement (p<0.001) for the HUMIRA/MTX combination therapy group versus either the MTX monotherapy or the HUMIRA monotherapy group at Week 52, which was maintained through Week 104.

14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of HUMIRA was assessed in two studies (Studies JIA-I and JIA-II) in patients with active polyarticular juvenile idiopathic arthritis (JIA).

Study JIA-I

The safety and efficacy of HUMIRA were assessed in a multicenter, randomized, withdrawal, double-blind, parallel-group study in 171 patients who were 4 to 17 years of age with polyarticular JIA. In the study, the patients were stratified into two groups: MTX-treated or non-MTX-treated. All patients had to show signs of active moderate or severe disease despite previous treatment with NSAIDs, analgesics, corticosteroids, or DMARDS. Patients who received prior treatment with any biologic DMARDS were excluded from the study.

The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomized withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, HUMIRA was administered based on body surface area at a dose of 24 mg/m^2 up to a maximum total body dose of 40 mg subcutaneously (SC) every other week. In the OLE-FD phase, the patients were treated with 20 mg of HUMIRA SC every other week if their weight was less than 30 kg and with 40 mg of HUMIRA SC every other week if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum).

Patients demonstrating a Pediatric ACR 30 response at the end of OL-LI phase were randomized into the double blind (DB) phase of the study and received either HUMIRA or placebo every other week for 32 weeks or until disease flare. Disease flare was defined as a worsening of ≥30% from baseline in ≥3 of 6 Pediatric ACR core criteria, ≥2 active joints, and improvement of >30% in no more than 1 of the 6 criteria. After 32 weeks or at the time of disease flare during the DB phase, patients were treated in the open-label extension phase based on the BSA regimen (OLE-BSA), before converting to a fixed dose regimen based on body weight (OLE-FD phase).

Study JIA-I Clinical Response

At the end of the 16-week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non-MTX stratum were Pediatric ACR 30 responders. In the DB phase significantly fewer patients who received HUMIRA experienced disease flare compared to placebo, both without MTX (43% *vs.* 71%) and with MTX (37% *vs.* 65%). More patients treated with HUMIRA continued to show pediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received HUMIRA throughout the study.

Study JIA-II

HUMIRA was assessed in an open-label, multicenter study in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with moderately to severely active polyarticular JIA. Most patients (97%) received at least 24 weeks of HUMIRA treatment dosed 24 mg/m^2 up to a maximum of 20 mg every other week as a single SC injection up to a maximum of 120 weeks duration. During the study, most patients used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs. The primary objective of the study was evaluation of safety *[see Adverse Reactions (6.1)]*.

14.3 Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis (PsA). Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg HUMIRA was administered every other week.

Study PsA-I enrolled 313 adult patients with moderately to severely active PsA (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of plaque psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric PsA (N=77); or (5) AS-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of ≤30 mg/week for >1 month) could continue MTX at the same dose. Doses of HUMIRA 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with HUMIRA resulted in improvements in the measures of disease activity (see Tables 7 and 8). Among patients with PsA who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks) and were maintained up to 88 weeks in the ongoing open-label study. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with

the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the HUMIRA group (N=69), compared to 1% and 0% respectively, in the placebo group (N=69) ($p<0.001$). PASI responses were apparent in some patients at the time of the first visit (two weeks). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Table 7. ACR Response in Study PsA-I (Percent of Patients)

	Placebo N=162	HUMIRA* N=151
ACR20		
Week 12	14%	58%
Week 24	15%	57%
ACR50		
Week 12	4%	36%
Week 24	6%	39%
ACR70		
Week 12	1%	20%
Week 24	1%	23%
* $p<0.001$ for all comparisons between HUMIRA and placebo		

Table 8. Components of Disease Activity in Study PsA-I

	Placebo N=162		HUMIRA* N=151	
Parameter: median	Baseline	24 weeks	Baseline	24 weeks
Number of tender joints[a]	23.0	17.0	20.0	5.0
Number of swollen joints[b]	11.0	9.0	11.0	3.0
Physician global assessment[c]	53.0	49.0	55.0	16.0
Patient global assessment[c]	49.5	49.0	48.0	20.0
Pain[c]	49.0	49.0	54.0	20.0
Disability index (HAQ)[d]	1.0	0.9	1.0	0.4
CRP (mg/dL)[e]	0.8	0.7	0.8	0.2

* $p<0.001$ for HUMIRA *vs.* placebo comparisons based on median changes

[a] Scale 0-78

[b] Scale 0-76

[c] Visual analog scale; 0=best, 100=worst

[d] Disability Index of the Health Assessment Questionnaire; 0=best, 3=worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[e]	Normal range: 0-0.287 mg/dL

Similar results were seen in an additional, 12-week study in 100 patients with moderate to severe psoriatic arthritis who had suboptimal response to DMARD therapy as manifested by ≥3 tender joints and ≥3 swollen joints at enrollment.

Radiographic Response

Radiographic changes were assessed in the PsA studies. Radiographs of hands, wrists, and feet were obtained at baseline and Week 24 during the double-blind period when patients were on HUMIRA or placebo and at Week 48 when all patients were on open-label HUMIRA. A modified Total Sharp Score (mTSS), which included distal interphalangeal joints (i.e., not identical to the TSS used for rheumatoid arthritis), was used by readers blinded to treatment group to assess the radiographs.

HUMIRA-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks (see Table 9).

Table 9. Change in Modified Total Sharp Score in Psoriatic Arthritis

	Placebo N=141	**HUMIRA N=133**	
	Week 24	Week 24	Week 48
Baseline mean	22.1	23.4	23.4
Mean Change ± SD	0.9 ± 3.1	-0.1 ± 1.7	-0.2 ± 4.9[*]
* <0.001 for the difference between HUMIRA, Week 48 and Placebo, Week 24 (primary analysis)			

Physical Function Response

In Study PsA-I, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 40 mg of HUMIRA every other week showed greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at Weeks 12 and 24 respectively) in comparison to placebo (mean decreases of 1% and 3% at Weeks 12 and 24 respectively). At Weeks 12 and 24, patients treated with HUMIRA showed greater improvement from baseline in the SF-36 Physical Component Summary score compared to patients treated with placebo, and no worsening in the SF-36 Mental Component Summary score. Improvement in physical function based on the HAQ-DI was maintained for up to 84 weeks through the open-label portion of the study.

14.4 Ankylosing Spondylitis

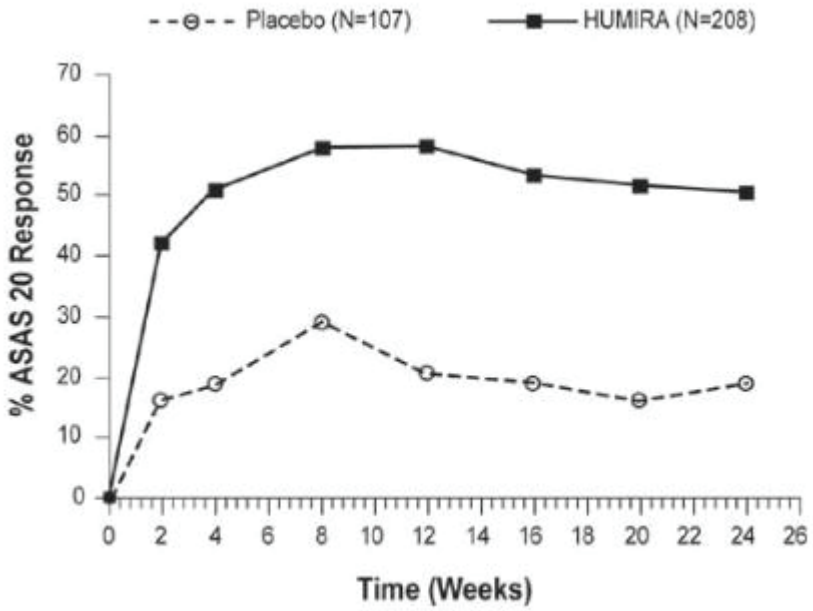
The safety and efficacy of HUMIRA 40 mg every other week was assessed in 315 adult patients in a randomized, 24 week double-blind, placebo-controlled study in patients with active ankylosing spondylitis (AS) who had an inadequate response to glucocorticoids, NSAIDs, analgesics, methotrexate or sulfasalazine. Active AS was defined as patients who fulfilled at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score ≥4 cm, (2) a visual analog score (VAS) for total back pain ≥ 40 mm, and (3) morning stiffness

≥ 1 hour. The blinded period was followed by an open-label period during which patients received HUMIRA 40 mg every other week subcutaneously for up to an additional 28 weeks.

Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 2 and Table 10.

Responses of patients with total spinal ankylosis (n=11) were similar to those without total ankylosis.

Figure 2. ASAS 20 Response By Visit, Study AS-I



At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving HUMIRA, compared to 21%, 10%, and 5% respectively, of patients receiving placebo ($p < 0.001$). Similar responses were seen at Week 24 and were sustained in patients receiving open-label HUMIRA for up to 52 weeks.

A greater proportion of patients treated with HUMIRA (22%) achieved a low level of disease activity at 24 weeks (defined as a value <20 [on a scale of 0 to 100 mm] in each of the four ASAS response parameters) compared to patients treated with placebo (6%).

Table 10. Components of Ankylosing Spondylitis Disease Activity

	Placebo N=107		HUMIRA N=208	
	Baseline mean	Week 24 mean	Baseline mean	Week 24 mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity[a*]	65	60	63	38

Total back pain*	67	58	65	37
Inflammation[b*]	6.7	5.6	6.7	3.6
BASFI[c*]	56	51	52	34
BASDAI[d] score*	6.3	5.5	6.3	3.7
BASMI[e] score*	4.2	4.1	3.8	3.3
Tragus to wall (cm)	15.9	15.8	15.8	15.4
Lumbar flexion (cm)	4.1	4.0	4.2	4.4
Cervical rotation (degrees)	42.2	42.1	48.4	51.6
Lumbar side flexion (cm)	8.9	9.0	9.7	11.7
Intermalleolar distance (cm)	92.9	94.0	93.5	100.8
CRP[f*]	2.2	2.0	1.8	0.6

[a] Percent of subjects with at least a 20% and 10-unit improvement measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe"
[b] mean of questions 5 and 6 of BASDAI (defined in 'd')
[c] Bath Ankylosing Spondylitis Functional Index
[d] Bath Ankylosing Spondylitis Disease Activity Index
[e] Bath Ankylosing Spondylitis Metrology Index
[f] C-Reactive Protein (mg/dL)
* statistically significant for comparisons between HUMIRA and placebo at Week 24

A second randomized, multicenter, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis showed similar results.

Patients treated with HUMIRA achieved improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.6 *vs.* -1.1) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (7.4 *vs.* 1.9) compared to placebo-treated patients at Week 24.

14.5 Adult Crohn's Disease

The safety and efficacy of multiple doses of HUMIRA were assessed in adult patients with moderately to severely active Crohn's disease, CD, (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted, and 79% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies. In Study CD-I, 299 TNF-blocker naïve patients were randomized to one of four treatment groups: the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2. Clinical results were assessed at Week 4.

In the second induction study, Study CD-II, 325 patients who had lost response to, or were intolerant to, previous infliximab therapy were randomized to receive either 160 mg HUMIRA at

Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4.

Maintenance of clinical remission was evaluated in Study CD-III. In this study, 854 patients with active disease received open-label HUMIRA, 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg HUMIRA every other week, 40 mg HUMIRA every week, or placebo. The total study duration was 56 weeks. Patients in clinical response (decrease in CDAI ≥70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4.

Induction of Clinical Remission

A greater percentage of the patients treated with 160/80 mg HUMIRA achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF blocker naïve (CD-I), or had lost response to or were intolerant to infliximab (CD-II) (see Table 11).

Table 11. Induction of Clinical Remission in Studies CD-I and CD-II (Percent of Patients)

	CD-I		**CD-II**	
	Placebo N=74	**HUMIRA 160/80 mg N=76**	**Placebo N=166**	**HUMIRA 160/80 mg N=159**
Week 4				
Clinical remission	12%	36%*	7%	21%*
Clinical response	34%	58%**	34%	52%**
Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points. * p<0.001 for HUMIRA *vs.* placebo pairwise comparison of proportions ** p<0.01 for HUMIRA *vs.* placebo pairwise comparison of proportions				

Maintenance of Clinical Remission

In Study CD-III at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. At Weeks 26 and 56, greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the HUMIRA 40 mg every other week maintenance group compared to patients in the placebo maintenance group (see Table 12). The group that received HUMIRA therapy every week did not demonstrate significantly higher remission rates compared to the group that received HUMIRA every other week.

Table 12. Maintenance of Clinical Remission in CD-III (Percent of Patients)

	Placebo	**40 mg HUMIRA every other week**
	N=170	**N=172**
Week 26		
Clinical remission	17%	40%*
Clinical response	28%	54%*
Week 56		

Clinical remission	12%	36%*
Clinical response	18%	43%*
Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points. *p<0.001 for HUMIRA vs. placebo pairwise comparisons of proportions		

Of those in response at Week 4 who attained remission during the study, patients in the HUMIRA every other week group maintained remission for a longer time than patients in the placebo maintenance group. Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.

14.6 Pediatric Crohn's Disease

A randomized, double-blind, 52-week clinical study of 2 dose levels of HUMIRA (Study PCD-I) was conducted in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease (defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30).[2] Enrolled patients had over the previous two year period an inadequate response to corticosteroids or an immunomodulator (i.e., azathioprine, 6-mercaptopurine, or methotrexate). Patients who had previously received a TNF blocker were allowed to enroll if they had previously had loss of response or intolerance to that TNF blocker.

Patients received open-label induction therapy at a dose based on their body weight (≥40 kg and <40 kg). Patients weighing ≥40 kg received 160 mg (at Week 0) and 80 mg (at Week 2). Patients weighing <40 kg received 80 mg (at Week 0) and 40 mg (at Week 2). At Week 4, patients within each body weight category (≥40 kg and <40 kg) were randomized 1:1 to one of two maintenance dose regimens (high dose and low dose). The high dose was 40 mg every other week for patients weighing ≥40 kg and 20 mg every other week for patients weighing <40 kg. The low dose was 20 mg every other week for patients weighing ≥40 kg and 10 mg every other week for patients weighing <40 kg.

Concomitant stable dosages of corticosteroids (prednisone dosage ≤40 mg/day or equivalent) and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted throughout the study.

At Week 12, patients who experienced a disease flare (increase in PCDAI of ≥ 15 from Week 4 and absolute PCDAI > 30) or who were non-responders (did not achieve a decrease in the PCDAI of ≥ 15 from baseline for 2 consecutive visits at least 2 weeks apart) were allowed to dose-escalate (i.e., switch from blinded every other week dosing to blinded every week dosing); patients who dose-escalated were considered treatment failures.

At baseline, 38% of patients were receiving corticosteroids, and 62% of patients were receiving an immunomodulator. Forty-four percent (44%) of patients had previously lost response or were intolerant to a TNF blocker. The median baseline PCDAI score was 40.

Of the 192 patients total, 188 patients completed the 4 week induction period, 152 patients completed 26 weeks of treatment, and 124 patients completed 52 weeks of treatment. Fifty-one percent (51%) (48/95) of patients in the low maintenance dose group dose-escalated, and 38% (35/93) of patients in the high maintenance dose group dose-escalated.

At Week 4, 28% (52/188) of patients were in clinical remission (defined as PCDAI ≤ 10).

The proportions of patients in clinical remission (defined as PCDAI ≤ 10) and clinical response (defined as reduction in PCDAI of at least 15 points from baseline) were assessed at Weeks 26 and 52.

At both Weeks 26 and 52, the proportion of patients in clinical remission and clinical response was numerically higher in the high dose group compared to the low dose group (Table 13). The recommended maintenance regimen is 20 mg every other week for patients weighing < 40 kg and 40 mg every other week for patients weighing ≥ 40 kg. Every week dosing is not the recommended maintenance dosing regimen *[see Dosage and Administration (2.4)]*.

Table 13. Clinical Remission and Clinical Response in Study PCD-I

	Low Maintenance Dose[†] (20 or 10 mg every other week) N = 95	**High Maintenance Dose[#] (40 or 20 mg every other week) N = 93**
Week 26		
Clinical Remission[‡]	28%	39%
Clinical Response[§]	48%	59%
Week 52		
Clinical Remission[‡]	23%	33%
Clinical Response[§]	28%	42%

[†]The low maintenance dose was 20 mg every other week for patients weighing ≥ 40 kg and 10 mg every other week for patients weighing < 40 kg.
[#]The high maintenance dose was 40 mg every other week for patients weighing ≥ 40 kg and 20 mg every other week for patients weighing < 40 kg.
[‡]Clinical remission defined as PCDAI ≤ 10.
[§]Clinical response defined as reduction in PCDAI of at least 15 points from baseline.

14.7 Ulcerative Colitis

The safety and efficacy of HUMIRA were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 on a 12 point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP in two randomized, double-blind, placebo-controlled clinical studies (Studies UC-I and UC-II). Both studies enrolled TNF-blocker naïve patients, but Study UC-II also allowed entry of patients who lost response to or were intolerant to TNF-blockers. Forty percent (40%) of patients enrolled in Study UC-II had previously used another TNF-blocker.

Concomitant stable doses of aminosalicylates and immunosuppressants were permitted. In Studies UC-I and II, patients were receiving aminosalicylates (69%), corticosteroids (59%) and/or azathioprine or 6-MP (37%) at baseline. In both studies, 92% of patients received at least one of these medications.

Induction of clinical remission (defined as Mayo score ≤ 2 with no individual subscores > 1) at Week 8 was evaluated in both studies. Clinical remission at Week 52 and sustained clinical remission (defined as clinical remission at both Weeks 8 and 52) were evaluated in Study UC-II.

In Study UC-I, 390 TNF-blocker naïve patients were randomized to one of three treatment groups for the primary efficacy analysis. The placebo group received placebo at Weeks 0, 2, 4 and 6. The 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, and the 80/40 group received 80 mg HUMIRA at Week 0 and 40 mg at Week 2. After Week 2, patients in both HUMIRA treatment groups received 40 mg every other week (eow).

In Study UC-II, 518 patients were randomized to receive either HUMIRA 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4 through Week 50, or placebo starting at Week 0 and eow through Week 50. Corticosteroid taper was permitted starting at Week 8.

In both Studies UC-I and UC-II, a greater percentage of the patients treated with 160/80 mg of HUMIRA compared to patients treated with placebo achieved induction of clinical remission. In Study UC-II, a greater percentage of the patients treated with 160/80 mg of HUMIRA compared to patients treated with placebo achieved sustained clinical remission (clinical remission at both Weeks 8 and 52) (Table 14).

Table 14. Induction of Clinical Remission in Studies UC-I and UC-II and Sustained Clinical Remission in Study UC-II (Percent of Patients)

	Study UC-I			**Study UC-II**		
	Placebo N=130	**HUMIRA 160/80 mg N=130**	**Treatment Difference (95% CI)**	**Placebo N=246**	**HUMIRA 160/80 mg N=248**	**Treatment Difference (95% CI)**
Induction of Clinical Remission (Clinical Remission at Week 8)	9.2%	18.5%	9.3%* (0.9%, 17.6%)	9.3%	16.5%	7.2%* (1.2%, 12.9%)
Sustained Clinical Remission (Clinical Remission at both Weeks 8 and 52)	N/A	N/A	N/A	4.1%	8.5%	4.4%* (0.1%, 8.6%)

Clinical remission is defined as Mayo score ≤ 2 with no individual subscores > 1.
CI=Confidence interval
* $p<0.05$ for HUMIRA *vs.* placebo pairwise comparison of proportions

In Study UC-I, there was no statistically significant difference in clinical remission observed between the HUMIRA 80/40 mg group and the placebo group at Week 8.

In Study UC-II, 17.3% (43/248) in the HUMIRA group were in clinical remission at Week 52 compared to 8.5% (21/246) in the placebo group (treatment difference: 8.8%; 95% confidence interval (CI): [2.8%, 14.5%]; $p<0.05$).

In the subgroup of patients in Study UC-II with prior TNF-blocker use, the treatment difference for induction of clinical remission appeared to be lower than that seen in the whole study

population, and the treatment differences for sustained clinical remission and clinical remission at Week 52 appeared to be similar to those seen in the whole study population. The subgroup of patients with prior TNF-blocker use achieved induction of clinical remission at 9% (9/98) in the HUMIRA group versus 7% (7/101) in the placebo group, and sustained clinical remission at 5% (5/98) in the HUMIRA group versus 1% (1/101) in the placebo group. In the subgroup of patients with prior TNF-blocker use, 10% (10/98) were in clinical remission at Week 52 in the HUMIRA group versus 3% (3/101) in the placebo group.

14.8 Plaque Psoriasis

The safety and efficacy of HUMIRA were assessed in randomized, double-blind, placebo-controlled studies in 1696 adult subjects with moderate to severe chronic plaque psoriasis (Ps) who were candidates for systemic therapy or phototherapy.

Study Ps-I evaluated 1212 subjects with chronic Ps with ≥10% body surface area (BSA) involvement, Physician's Global Assessment (PGA) of at least moderate disease severity, and Psoriasis Area and Severity Index (PASI) ≥12 within three treatment periods. In period A, subjects received placebo or HUMIRA at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, subjects who achieved at least a PASI 75 response at Week 16, defined as a PASI score improvement of at least 75% relative to baseline, entered period B and received open-label 40 mg HUMIRA every other week. After 17 weeks of open label therapy, subjects who maintained at least a PASI 75 response at Week 33 and were originally randomized to active therapy in period A were re-randomized in period C to receive 40 mg HUMIRA every other week or placebo for an additional 19 weeks. Across all treatment groups the mean baseline PASI score was 19 and the baseline Physician's Global Assessment score ranged from "moderate" (53%) to "severe" (41%) to "very severe" (6%).

Study Ps-II evaluated 99 subjects randomized to HUMIRA and 48 subjects randomized to placebo with chronic plaque psoriasis with ≥10% BSA involvement and PASI ≥12. Subjects received placebo, or an initial dose of 80 mg HUMIRA at Week 0 followed by 40 mg every other week starting at Week 1 for 16 weeks. Across all treatment groups the mean baseline PASI score was 21 and the baseline PGA score ranged from "moderate" (41%) to "severe" (51%) to "very severe" (8%).

Studies Ps-I and II evaluated the proportion of subjects who achieved "clear" or "minimal" disease on the 6-point PGA scale and the proportion of subjects who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 (see Table 15 and 16).

Additionally, Study Ps-I evaluated the proportion of subjects who maintained a PGA of "clear" or "minimal" disease or a PASI 75 response after Week 33 and on or before Week 52.

Table 15. Efficacy Results at 16 Weeks in Study Ps-I Number of Subjects (%)

	HUMIRA 40 mg every other week	Placebo
	N = 814	N = 398
PGA: Clear or minimal*	506 (62%)	17 (4%)
PASI 75	578 (71%)	26 (7%)
* Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red		

coloration Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration

Table 16. Efficacy Results at 16 Weeks in Study Ps-II Number of Subjects (%)

	HUMIRA 40 mg every other week	Placebo
	N = 99	N = 48
PGA: Clear or minimal*	70 (71%)	5 (10%)
PASI 75	77 (78%)	9 (19%)
* Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red coloration Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration		

Additionally, in Study Ps-I, subjects on HUMIRA who maintained a PASI 75 were re-randomized to HUMIRA (N = 250) or placebo (N = 240) at Week 33. After 52 weeks of treatment with HUMIRA, more subjects on HUMIRA maintained efficacy when compared to subjects who were re-randomized to placebo based on maintenance of PGA of "clear" or "minimal" disease (68% *vs.* 28%) or a PASI 75 (79% *vs.* 43%).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA "moderate" or worse) was approximately 5 months. During the withdrawal period, no subject experienced transformation to either pustular or erythrodermic psoriasis. A total of 178 subjects who relapsed re-initiated treatment with 80 mg of HUMIRA, then 40 mg eow beginning at week 1. At week 16, 69% (123/178) of subjects had a response of PGA "clear" or "minimal".

14.9 Hidradenitis Suppurativa

Two randomized, double-blind, placebo-controlled studies (Studies HS-I and II) evaluated the safety and efficacy of HUMIRA in a total of 633 adult subjects with moderate to severe hidradenitis suppurativa (HS) with Hurley Stage II or III disease and with at least 3 abscesses or inflammatory nodules. In both studies, subjects received placebo or HUMIRA at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 and continued through Week 11. Subjects used topical antiseptic wash daily. Concomitant oral antibiotic use was allowed in Study HS-II.

Both studies evaluated Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to baseline (see Table 17). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

In both studies, a higher proportion of HUMIRA- than placebo-treated subjects achieved HiSCR (see Table 17).

Table 17. Efficacy Results at 12 Weeks in Subjects with Moderate to Severe Hidradenitis Suppurativa

	HS Study I		HS Study II*	
	Placebo	**Humira 40 mg Weekly**	**Placebo**	**Humira 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)	N = 154 40 (26%)	N = 153 64 (42%)	N=163 45 (28%)	N=163 96 (59%)
*19.3% of subjects in Study HS-II continued baseline oral antibiotic therapy during the study.				

In both studies, from Week 12 to Week 35 (Period B), subjects who had received HUMIRA were re-randomized to 1 of 3 treatment groups (HUMIRA 40 mg every week, HUMIRA 40 mg every other week, or placebo). Subjects who had been randomized to placebo were assigned to receive HUMIRA 40 mg every week (Study HS-I) or placebo (Study HS-II).

During Period B, flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

14.10 Uveitis

The safety and efficacy of HUMIRA were assessed in adult patients with non-infectious intermediate, posterior and panuveitis excluding patients with isolated anterior uveitis, in two randomized, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or HUMIRA at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. The primary efficacy endpoint in both studies was ´time to treatment failure´.

Treatment failure was a multi-component outcome defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in anterior chamber (AC) cell grade or vitreous haze (VH) grade or a decrease in best corrected visual acuity (BCVA).

Study UV I evaluated 217 patients with active uveitis while being treated with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a standardized dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study UV II evaluated 226 patients with inactive uveitis while being treated with corticosteroids (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with HUMIRA versus patients receiving placebo. In both studies, all

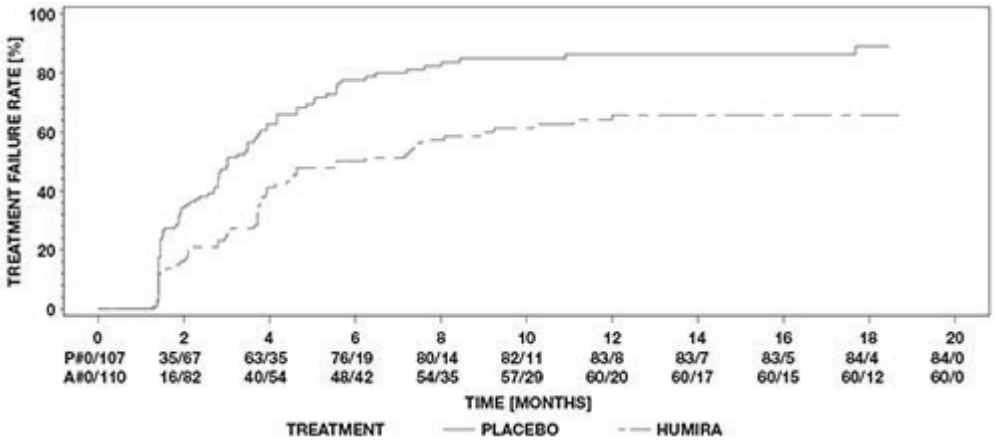
components of the primary endpoint contributed cumulatively to the overall difference between HUMIRA and placebo groups (Table 18).

Table 18. Time to Treatment Failure in Studies UV I and UV II

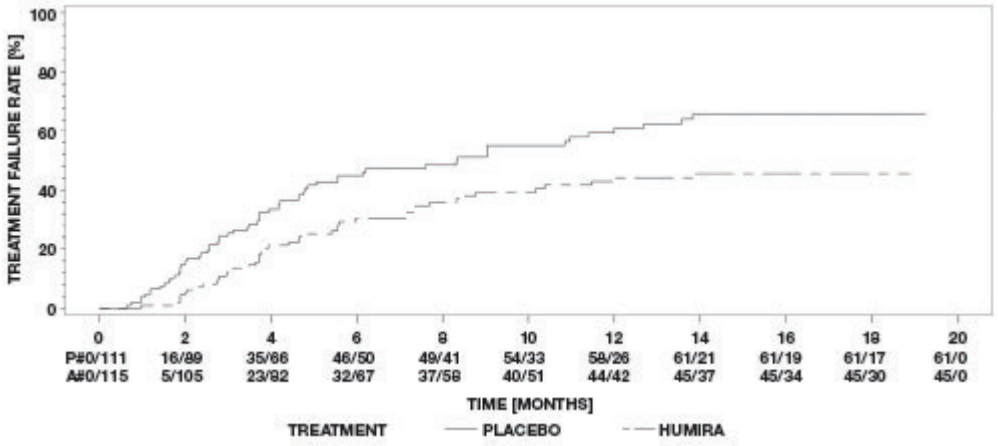
	UV I			UV II		
	Placebo (N = 107)	HUMIRA (N = 110)	HR [95% CI][a]	Placebo (N = 111)	HUMIRA (N = 115)	HR [95% CI][a]
Failure[b] n (%)	84 (78.5)	60 (54.5)	0.50 [0.36, 0.70]	61 (55.0)	45 (39.1)	0.57 [0.39, 0.84]
Median Time to Failure (Months) [95% CI]	3.0 [2.7, 3.7]	5.6 [3.9, 9.2]	N/A	8.3 [4.8, 12.0]	NE[c]	N/A

[a] HR of HUMIRA versus placebo from proportional hazards regression with treatment as factor.
[b] Treatment failure at or after Week 6 in Study UV I, or at or after Week 2 in Study UV II, was counted as event. Subjects who discontinued the study were censored at the time of dropping out.
[c] NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 3: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)



Study UV I



Study UV II

Note: P# = Placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk).

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 17 Registries, 2000-2007.
2. Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr. 1991;12:439-447.

16 HOW SUPPLIED/STORAGE AND HANDLING

HUMIRA® (adalimumab) is supplied as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available.

- **HUMIRA Pen Carton - 40 mg/0.8 mL**
  HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-4339-02.
- **HUMIRA Pen Carton - 40 mg/0.4 mL**
  HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.4 mL of HUMIRA. The black needle cover is not made with natural rubber latex. The NDC number is 0074-0554-02.
- **HUMIRA Pen 40 mg/0.8 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa**
  HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge,

½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-4339-06.

- **HUMIRA Pen 40 mg/0.4 mL - Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa**
  HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Starter Package for Crohn's Disease, Ulcerative Colitis or Hidradenitis Suppurativa). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.4 mL of HUMIRA. The black needle cover is not made with natural rubber latex. The NDC number is 0074-0554-06.
- **HUMIRA Pen 40 mg/0.8 mL - Psoriasis/Uveitis Starter Package**
  HUMIRA is dispensed in a carton containing 4 alcohol preps and 4 dose trays (Psoriasis/Uveitis Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-4339-07.
- **HUMIRA Pen 40 mg/0.4 mL - Psoriasis/Uveitis Starter Package**
  HUMIRA is dispensed in a carton containing 4 alcohol preps and 4 dose trays (Psoriasis/Uveitis Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.4 mL of HUMIRA. The black needle cover is not made with natural rubber latex. The NDC number is 0074-0554-04.
- **Prefilled Syringe Carton - 40 mg/0.8 mL**
  HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-3799-02.
- **Prefilled Syringe Carton - 40 mg/0.4 mL**
  HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 29 gauge thin wall, ½ inch needle, providing 40 mg/0.4 mL of HUMIRA. The black needle cover is not made with natural rubber latex. The NDC number is 0074-0243-02.
- **Prefilled Syringe Carton - 20 mg/0.4 mL**
  HUMIRA is supplied in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge, ½ inch needle, providing 20 mg/0.4 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-9374-02.
- **Prefilled Syringe Carton - 10 mg/0.2 mL**
  HUMIRA is supplied in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge, ½ inch needle, providing 10 mg/0.2 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-6347-02.

- **HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (6 count)**
  HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Pediatric Starter Package). Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-3799-06.
- **HUMIRA Prefilled Syringe 40 mg/0.8 mL - Pediatric Crohn's Disease Starter Package (3 count)**
  HUMIRA is dispensed in a carton containing 4 alcohol preps and 3 dose trays (Pediatric Starter Package). Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, ½ inch needle, providing 40 mg/0.8 mL of HUMIRA. The gray needle cover contains natural rubber latex. The NDC number is 0074-3799-03.
- **Single-Use Institutional Use Vial Carton - 40 mg/0.8 mL**
  HUMIRA is supplied for institutional use only in a carton containing a single-use, glass vial, providing 40 mg/0.8 mL of HUMIRA. The vial stopper is not made with natural rubber latex. The NDC number is 0074-3797-01.

Storage and Stability

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed.

Store in original carton until time of administration to protect from light.

If needed, for example when traveling, HUMIRA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. HUMIRA should be discarded if not used within the 14-day period. Record the date when HUMIRA is first removed from the refrigerator in the spaces provided on the carton and dose tray.

Do not store HUMIRA in extreme heat or cold.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.

- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the gray needle cap of the 27 gauge HUMIRA Pen and prefilled syringe contains natural rubber latex *[see How Supplied/Storage and Handling (16) for specific information]*.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

Instructions on Injection Technique

Inform patients that the first injection is to be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, instruct them in injection techniques and assess their ability to inject subcutaneously to ensure the proper administration of HUMIRA *[see Instructions for Use]*.

For patients who will use the HUMIRA Pen, tell them that they:

- Will hear a **loud 'click'** when the plum-colored activator button is pressed. The loud click means the **start** of the injection.
- Must keep holding the HUMIRA Pen against their squeezed, raised skin until all of the medicine is injected. This can take up to 10 seconds.
- Will know that the injection has finished when the yellow marker fully appears in the window view and stops moving.

Instruct patients to dispose of their used needles and syringes or used Pen in a FDA-cleared sharps disposal container immediately after use. **Instruct patients not to dispose of loose needles and syringes or Pen in their household trash.** Instruct patients that if they do not have a FDA-cleared sharps disposal container, they may use a household container that is made of a heavy-duty plastic, can be closed with a tight-fitting and puncture-resistant lid without sharps being able to come out, upright and stable during use, leak-resistant, and properly labeled to warn of hazardous waste inside the container.

Instruct patients that when their sharps disposal container is almost full, they will need to follow their community guidelines for the correct way to dispose of their sharps disposal container. Instruct patients that there may be state or local laws regarding disposal of used needles and syringes. Refer patients to the FDA's website at http://www.fda.gov/safesharpsdisposal for more information about safe sharps disposal, and for specific information about sharps disposal in the state that they live in.

Instruct patients not to dispose of their used sharps disposal container in their household trash unless their community guidelines permit this. Instruct patients not to recycle their used sharps disposal container.

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

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MEDICATION GUIDE
HUMIRA® (Hu-MARE-ah)
(adalimumab)
injection

Read the Medication Guide that comes with HUMIRA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about HUMIRA?

HUMIRA is a medicine that affects your immune system. HUMIRA can lower the ability of your immune system to fight infections. **Serious infections have happened in people taking HUMIRA. These serious infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some people have died from these infections.**

- Your doctor should test you for TB before starting HUMIRA.
- Your doctor should check you closely for signs and symptoms of TB during treatment with HUMIRA.

You should not start taking HUMIRA if you have any kind of infection unless your doctor says it is okay.

Before starting HUMIRA, tell your doctor if you:

- think you have an infection or have symptoms of infection such as:
  - fever, sweats, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
  - weight loss
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes
- have TB, or have been in close contact with someone with TB
- were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your doctor if you are not sure.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use HUMIRA. Ask your doctor if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B
- use the medicine ORENCIA® (abatacept), KINERET® (anakinra), RITUXAN® (rituximab), IMURAN® (azathioprine), or PURINETHOL® (6–mercaptopurine, 6-MP).
- are scheduled to have major surgery

After starting HUMIRA, call your doctor right away if you have an infection, or any sign of

an infection.
HUMIRA can make you more likely to get infections or make any infection that you may have worse.

Cancer

- For children and adults taking TNF-blockers, including HUMIRA, the chances of getting cancer may increase.
- There have been cases of unusual cancers in children, teenagers, and young adults using TNF-blockers.
- People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
- If you use TNF blockers including HUMIRA your chance of getting two types of skin cancer may increase (basal cell cancer and squamous cell cancer of the skin). These types of cancer are generally not life-threatening if treated. Tell your doctor if you have a bump or open sore that doesn't heal.
- Some people receiving TNF blockers including HUMIRA developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with another medicine called IMURAN® (azathioprine) or PURINETHOL® (6-mercaptopurine, 6–MP).

What is HUMIRA?

HUMIRA is a medicine called a Tumor Necrosis Factor (TNF) blocker. HUMIRA is used:

- To reduce the signs and symptoms of:
  - **moderate to severe rheumatoid arthritis (RA) in adults.** HUMIRA can be used alone, with methotrexate, or with certain other medicines.
  - **moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children** 2 years and older. HUMIRA can be used alone, with methotrexate, or with certain other medicines.
  - **psoriatic arthritis (PsA) in adults.** HUMIRA can be used alone or with certain other medicines.
  - **ankylosing spondylitis (AS) in adults.**
  - **moderate to severe Crohn's disease (CD) in adults** when other treatments have not worked well enough.
  - **moderate to severe Crohn's disease (CD) in children** 6 years and older when other treatments have not worked well enough.
  - **moderate to severe hidradenitis suppurativa (HS) in adults.**
- In adults, to help get **moderate to severe ulcerative colitis (UC)** under control (induce remission) and keep it under control (sustain remission) when certain other medicines have not worked well enough. It is not known if HUMIRA is effective in people who stopped responding to or could not tolerate TNF-blocker medicines.
- **To treat moderate to severe chronic (lasting a long time) plaque psoriasis (Ps) in adults** who have the condition in many areas of their body and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).
- **To treat non-infectious intermediate, posterior and panuveitis (UV) in adults.**

What should I tell my doctor before taking HUMIRA?

HUMIRA may not be right for you. Before starting HUMIRA, tell your doctor about all of your health conditions, including if you:

- have an infection. See **"What is the most important information I should know about HUMIRA?"**

- have or have had cancer.
- have any numbness or tingling or have a disease that affects your nervous system such as multiple sclerosis or Guillain-Barré syndrome.
- have or had heart failure.
- have recently received or are scheduled to receive a vaccine. You may receive vaccines, except for live vaccines while using HUMIRA. Children should be brought up to date with all vaccines before starting HUMIRA.
- are allergic to rubber or latex. Tell your doctor if you have any allergies to rubber or latex.
  - The gray needle cover for the HUMIRA Pen 40 mg/0.8 mL, HUMIRA 40 mg/0.8 mL prefilled syringe, HUMIRA 20 mg/0.4 mL prefilled syringe, and HUMIRA 10 mg/0.2 mL prefilled syringe contains natural rubber or latex.
  - The black needle cover for the HUMIRA Pen 40 mg/0.4 mL, HUMIRA 40 mg/0.4 mL prefilled syringe and the vial stopper on the HUMIRA institutional use vial are not made with natural rubber or latex.
- are allergic to HUMIRA or to any of its ingredients. See the end of this Medication Guide for a list of ingredients in HUMIRA.
- are pregnant or plan to become pregnant. It is not known if HUMIRA will harm your unborn baby. HUMIRA should only be used during a pregnancy if needed.
- have a baby and you were using HUMIRA during your pregnancy. Tell your baby's doctor before your baby receives any vaccines.
- breastfeeding or plan to breastfeed. You and your doctor should decide if you will breastfeed or use HUMIRA. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your doctor if you use:

- ORENCIA® (abatacept), KINERET® (anakinra), REMICADE® (infliximab), ENBREL® (etanercept), CIMZIA® (certolizumab pegol) or SIMPONI® (golimumab), because you should not use HUMIRA while you are also using one of these medicines.
- RITUXAN® (rituximab). Your doctor may not want to give you HUMIRA if you have received RITUXAN® (rituximab) recently.
- IMURAN® (azathioprine) or PURINETHOL® (6–mercaptopurine, 6-MP).

Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take HUMIRA?

- HUMIRA is given by an injection under the skin. Your doctor will tell you how often to take an injection of HUMIRA. This is based on your condition to be treated. **Do not inject HUMIRA more often than you were prescribed.**
- See the **Instructions for Use** inside the carton for complete instructions for the right way to prepare and inject HUMIRA.
- Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or 1-800-4HUMIRA (1-800-448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection after they have been shown how to prepare and inject HUMIRA.
- **Do not** try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA.
- Do not miss any doses of HUMIRA unless your doctor says it is okay. If you forget to take HUMIRA, inject a dose as soon as you remember. Then, take your next dose at your

regular scheduled time. This will put you back on schedule. In case you are not sure when to inject HUMIRA, call your doctor or pharmacist.
- If you take more HUMIRA than you were told to take, call your doctor.

What are the possible side effects of HUMIRA?
HUMIRA can cause serious side effects, including:
See "What is the most important information I should know about HUMIRA?"

- **Serious Infections.**
  Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with HUMIRA and during treatment with HUMIRA. Even if your TB test is negative your doctor should carefully monitor you for TB infections while you are taking HUMIRA. People who had a negative TB skin test before receiving HUMIRA have developed active TB. Tell your doctor if you have any of the following symptoms while taking or after taking HUMIRA:
    - cough that does not go away
    - low grade fever
    - weight loss
    - loss of body fat and muscle (wasting)
- **Hepatitis B infection in people who carry the virus in their blood.**
  If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use HUMIRA. Your doctor should do blood tests before you start treatment, while you are using HUMIRA, and for several months after you stop treatment with HUMIRA. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:
    - muscle aches
    - feel very tired
    - dark urine
    - skin or eyes look yellow
    - little or no appetite
    - vomiting
    - clay-colored bowel movements
    - fever
    - chills
    - stomach discomfort
    - skin rash
- **Allergic reactions.** Allergic reactions can happen in people who use HUMIRA. Call your doctor or get medical help right away if you have any of these symptoms of a serious allergic reaction:
    - hives
    - trouble breathing
    - swelling of your face, eyes, lips or mouth
- **Nervous system problems.** Signs and symptoms of a nervous system problem include: numbness or tingling, problems with your vision, weakness in your arms or legs, and dizziness.
- **Blood problems.** Your body may not make enough of the blood cells that help fight infections or help to stop bleeding. Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.
- **New heart failure or worsening of heart failure you already have. Call your doctor right away** if you get new worsening symptoms of heart failure while taking HUMIRA, including:
    - shortness of breath
    - sudden weight gain
    - swelling of your ankles or feet
- **Immune reactions including a lupus-like syndrome.** Symptoms include chest discomfort or pain that does not go away, shortness of breath, joint pain, or a rash on your cheeks or arms that gets worse in the sun. Symptoms may improve when you stop HUMIRA.

- **Liver Problems.** Liver problems can happen in people who use TNF-blocker medicines. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:
  - feel very tired
  - poor appetite or vomiting
  - skin or eyes look yellow
  - pain on the right side of your stomach (abdomen)
- **Psoriasis.** Some people using HUMIRA had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps that are filled with pus. Your doctor may decide to stop your treatment with HUMIRA.

Call your doctor or get medical care right away if you develop any of the above symptoms. Your treatment with HUMIRA may be stopped.

Common side effects with HUMIRA include:

- injection site reactions: redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. Call your doctor right away if you have pain, redness or swelling around the injection site that does not go away within a few days or gets worse.
- upper respiratory infections (including sinus infections)
- headaches
- rash

These are not all the possible side effects with HUMIRA. Tell your doctor if you have any side effect that bothers you or that does not go away. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store HUMIRA?

- Store HUMIRA in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC). Store HUMIRA in the original carton until use to protect it from light.
- **Do not freeze HUMIRA.** Do not use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray, Pen or prefilled syringe. Do not use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to 14 days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within 14 days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- Do not use a Pen or prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.

Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

General information about the safe and effective use of HUMIRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HUMIRA for a condition for which it was not prescribed. Do not give HUMIRA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about HUMIRA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about HUMIRA that is written for health professionals. For more information go to www.HUMIRA.com or you can enroll in a patient support program by calling 1-800-4HUMIRA

(1-800-448-6472).

What are the ingredients in HUMIRA?
Active ingredient: adalimumab

HUMIRA Pen 40 mg/0.8 mL, HUMIRA 40 mg/0.8 mL prefilled syringe, HUMIRA 20 mg/0.4 mL prefilled syringe, HUMIRA 10 mg/0.2 mL prefilled syringe, and HUMIRA 40 mg/0.8 mL institutional use vial:

Inactive ingredients: citric acid monohydrate, dibasic sodium phosphate dihydrate, mannitol, monobasic sodium phosphate dihydrate, polysorbate 80, sodium chloride, sodium citrate and Water for Injection. Sodium hydroxide is added as necessary to adjust pH.

HUMIRA Pen 40 mg/0.4 mL and HUMIRA 40 mg/0.4 mL prefilled syringe:

Inactive ingredients: mannitol, polysorbate 80, and Water for Injection.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 06/2016

03-B352

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

40 MG/0.8 ML

SINGLE-USE PEN

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HUMIRA.

IMPORTANT:

- Do not use HUMIRA if frozen, even if it has been thawed.
- The HUMIRA Pen contains glass. Do not drop or crush the Pen because the glass inside may break.
- Do not remove the gray cap or the plum-colored cap until right before your injection.
- When the plum-colored button on the HUMIRA Pen is pressed to give your dose of HUMIRA, you will hear a loud “click” sound.
    - You must practice injecting HUMIRA with your doctor or nurse so that you are not startled by this click when you start giving yourself the injections at home.

- The loud click sound means the start of the injection.
- You will know that the injection has finished when the yellow marker appears fully in the window view and stops moving.

See the section below called **"Prepare the HUMIRA Pen"**.

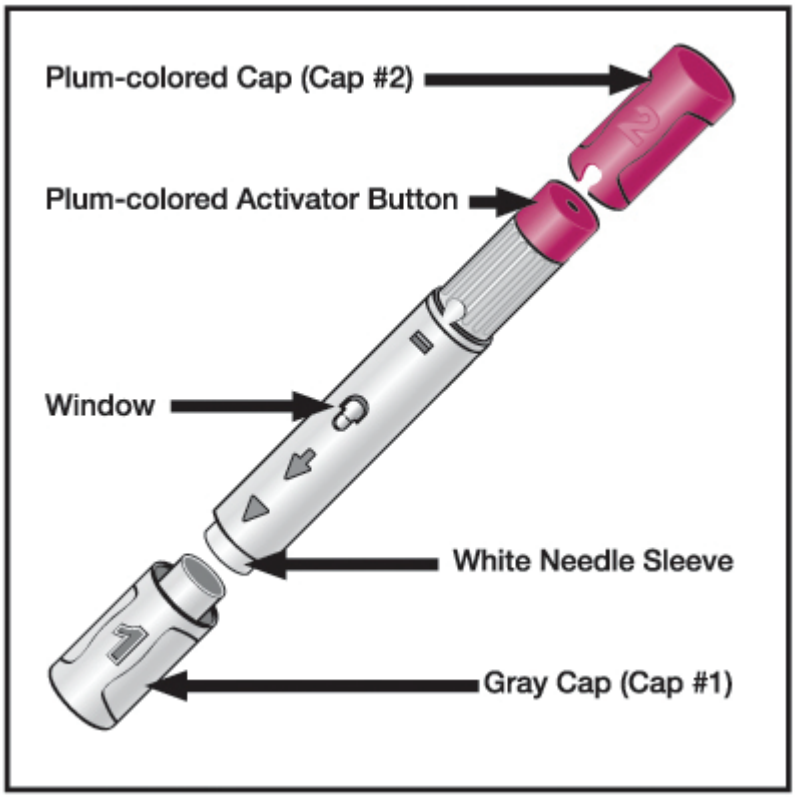
Gather the Supplies for Your Injection

- You will need the following supplies for each injection of HUMIRA.
  Find a clean, flat surface to place the supplies on.
  - 1 alcohol swab
  - 1 cotton ball or gauze pad (not included in your HUMIRA carton)
  - 1 HUMIRA Pen (See Figure A)
  - FDA-cleared sharps disposal container for HUMIRA Pen disposal (not included in your HUMIRA carton)

If more comfortable, take your HUMIRA Pen out of the refrigerator **15 to 30 minutes** before injecting to allow the liquid to reach room temperature. **Do not** remove the gray or plum-colored caps while allowing it to reach room temperature. **Do not** warm HUMIRA in any other way (for example, **do not** warm it in a microwave or in hot water).

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist. The diagram below shows what the HUMIRA Pen looks like. See Figure A.

Figure A



Check the carton, dose tray, and HUMIRA Pen.

1. Make sure the name HUMIRA appears on the carton, dose tray, and HUMIRA Pen label.

2. **Do not use** and **do call** your doctor or pharmacist if:
   - you drop or crush your HUMIRA Pen.
   - the seals on the top or bottom of the carton are broken or missing.
   - the expiration date on the carton, dose tray, and Pen has passed.
   - the HUMIRA Pen has been frozen or left in direct sunlight.
   - HUMIRA has been kept at room temperature for longer than **14** days or HUMIRA has been stored above 77°F (25°C).

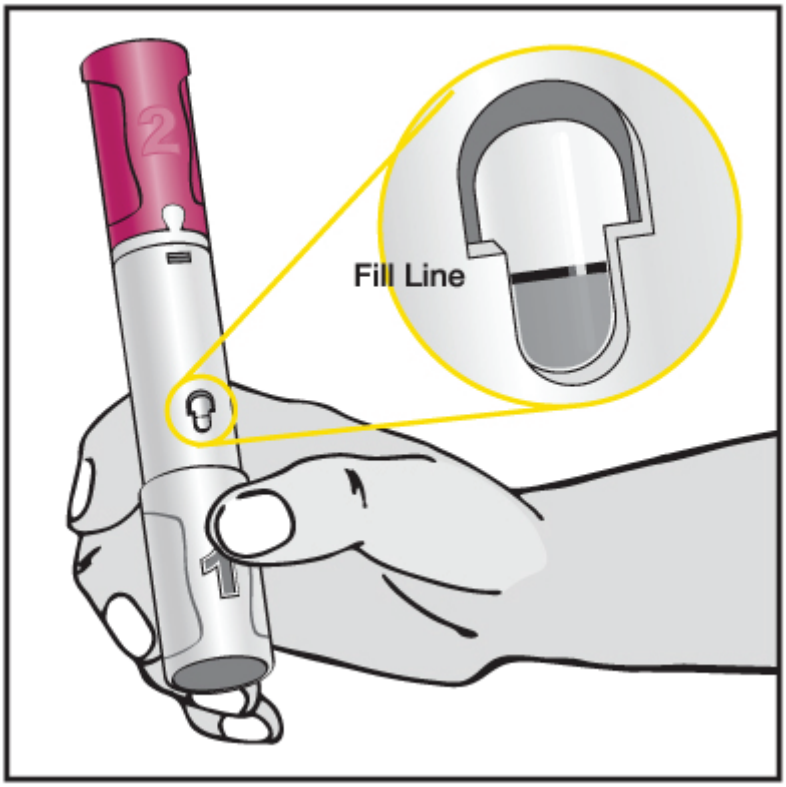
See the **"How should I store HUMIRA?"** section at the end of this Instructions for Use.

3. Hold the Pen with the gray cap (Cap # 1) pointed down.

4. Make sure the amount of liquid in the Pen is at the fill line or close to the fill line seen through the window. This is the full dose of HUMIRA that you will inject. See Figure B.

5. If the Pen does not have the full amount of liquid, **do not use that Pen**. Call your pharmacist.

Figure B

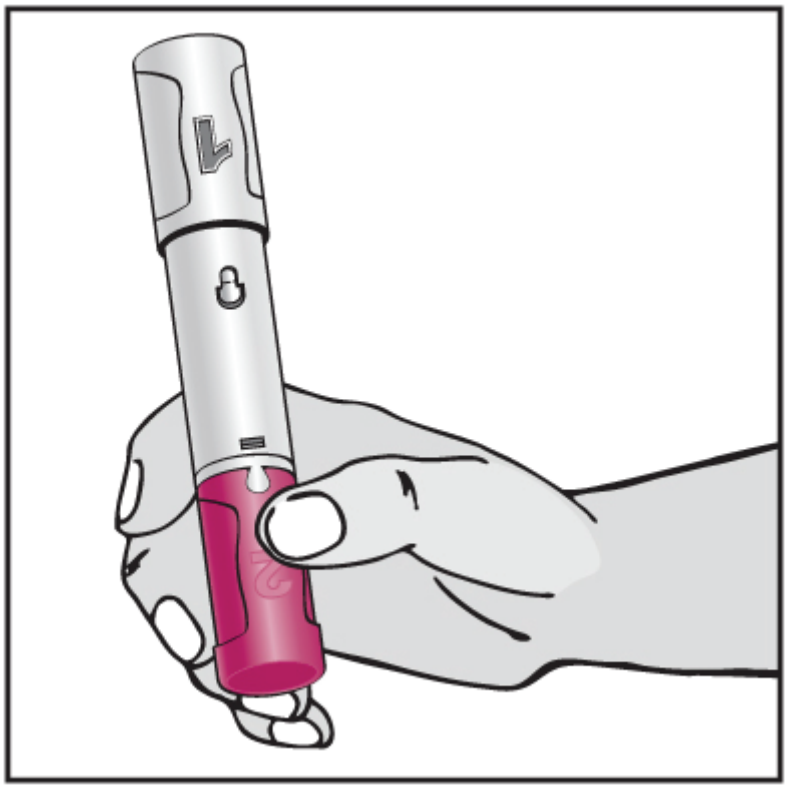


6. Turn the Pen over and hold the Pen with the gray cap (Cap # 1) pointed up. See Figure C.

7. Check the solution through the windows on the side of the Pen to make sure the liquid is clear and colorless. **Do not use** your HUMIRA Pen if the liquid is cloudy, discolored, or if it has

flakes or particles in it. Call your pharmacist. It is normal to see one or more bubbles in the window.

Figure C

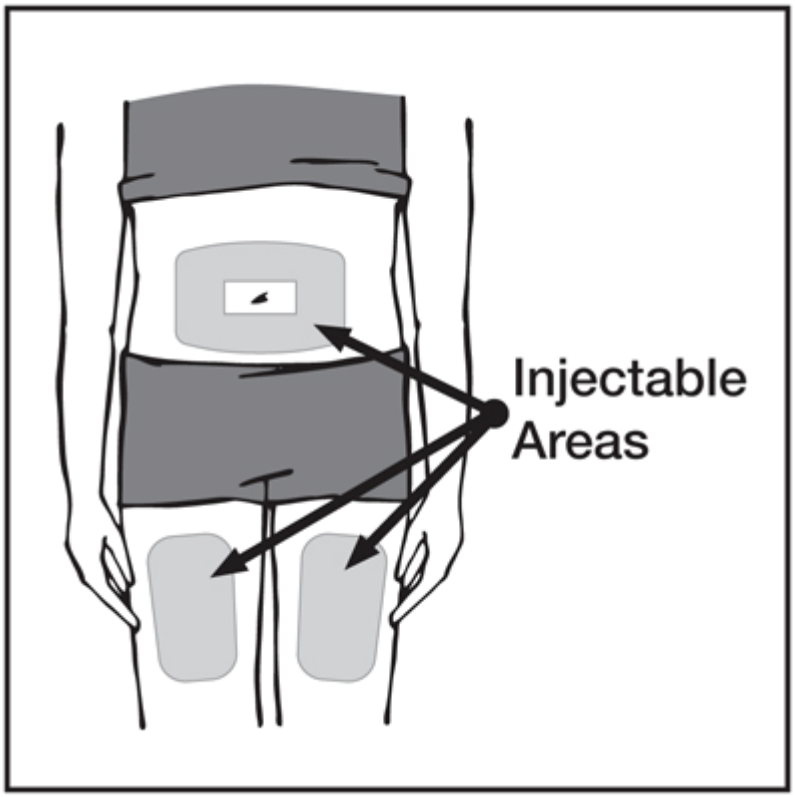


Choose the Injection Site

8. Wash and dry your hands well.

9. Choose an injection site on:
   - the front of your thighs or
   - your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure D.

Figure D



- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
- **Do not** inject HUMIRA into skin that is:
  - sore (tender)
  - bruised
  - red
  - hard
  - scarred or where you have stretch marks
- If you have psoriasis, **do not** inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

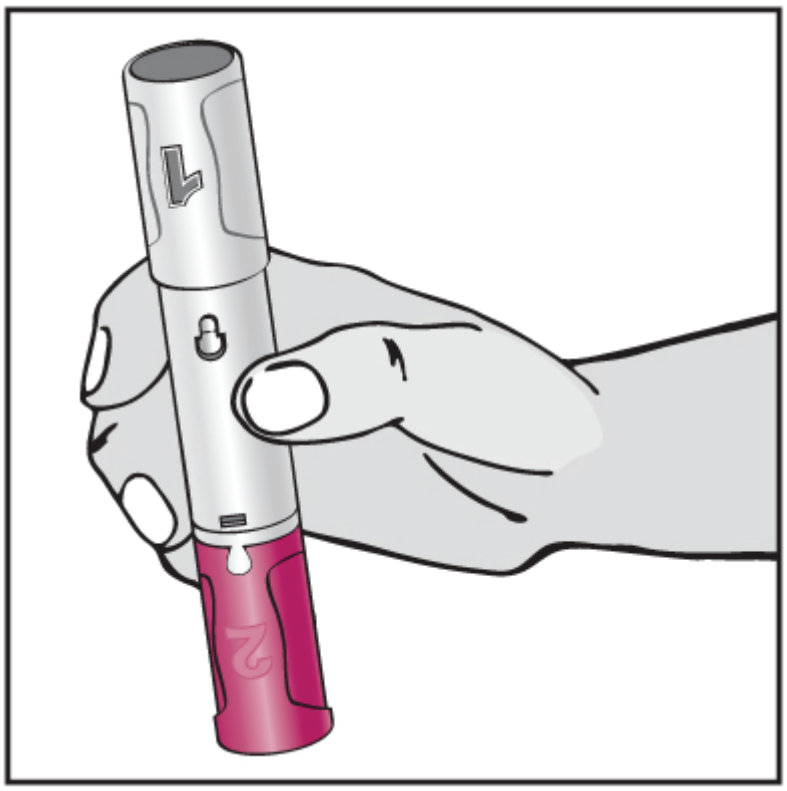
10. Wipe the injection site with an alcohol prep (swab) using a circular motion.
- **Do not** touch this area again before giving the injection. Allow the skin to dry before injecting. **Do not** fan or blow on the clean area.

Preparing the HUMIRA Pen

11. **Do not remove the gray cap (Cap # 1) or the plum-colored cap (Cap # 2) until right before your injection.**

12. Hold the middle of the Pen (gray body) with one hand so that you are not touching the gray cap (Cap # 1) or the plum-colored cap (Cap # 2). Turn the Pen so that the gray cap (Cap # 1) is pointing up. See Figure E.

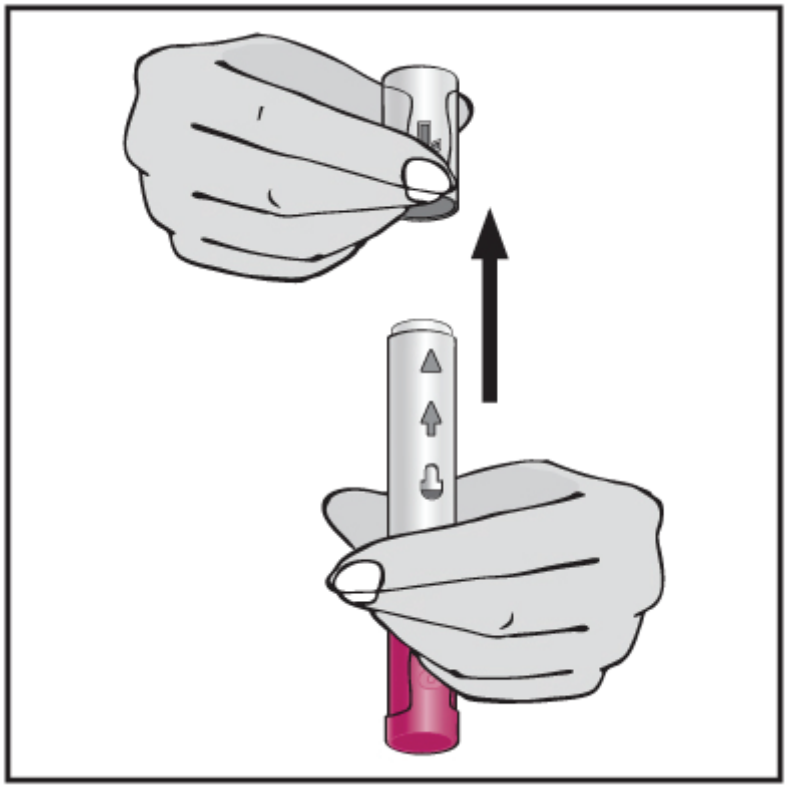
Figure E



13. With your other hand, pull the gray cap (Cap # 1) straight off (do not twist the cap). Make sure the small gray needle cover of the syringe has come off with the gray cap (Cap # 1). See Figure F.

14. Throw away the gray cap (Cap # 1).

Figure F



- **Do not** put the gray cap (Cap # 1) back on the Pen. Putting the gray cap (Cap # 1) back on may damage the needle.
- The white needle sleeve, which covers the needle, can now be seen.
- **Do not** touch the needle with your fingers or let the needle touch anything.
- You may see a few drops of liquid come out of the needle. This is normal.

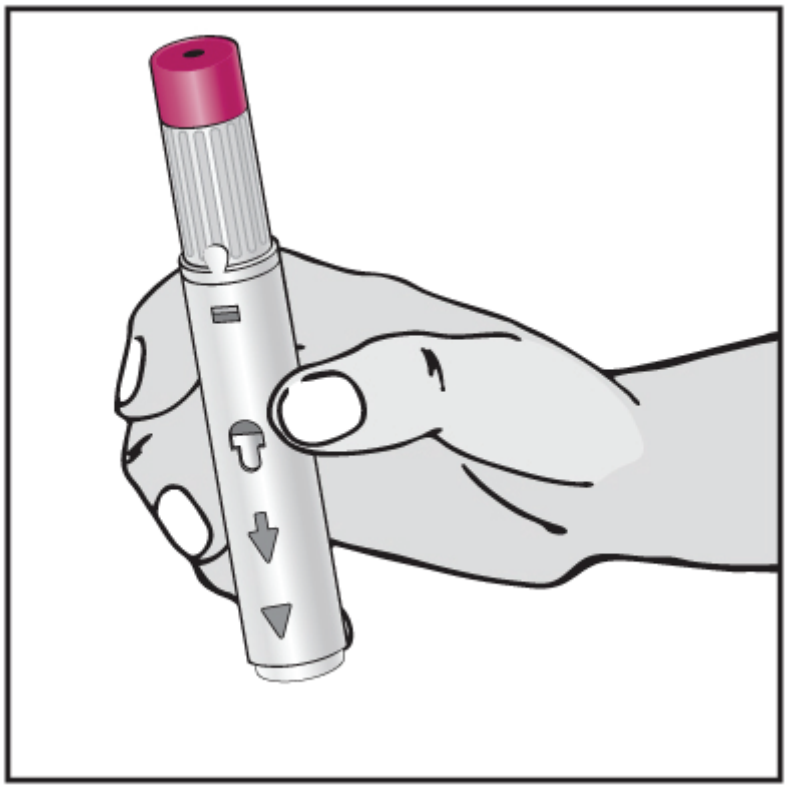
15. Remove the plum-colored cap (Cap # 2) from the bottom of the Pen by pulling it straight off (do not twist the cap). The Pen is now activated. Throw away the plum-colored cap.

- Do not put the plum-colored cap (Cap # 2) back on the Pen because it could cause medicine to come out of the syringe.

The plum-colored activator button:

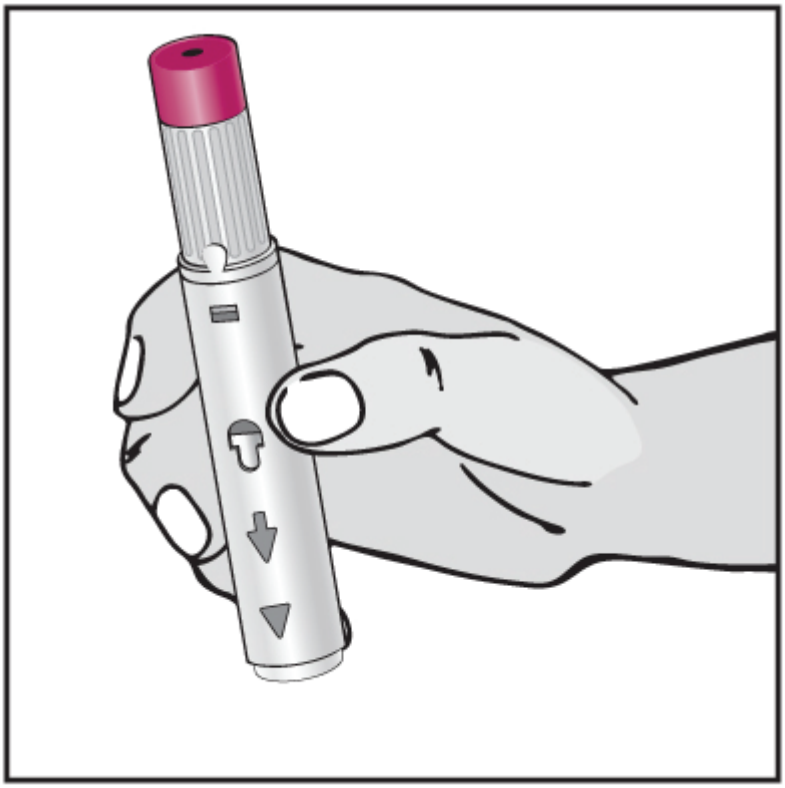
- Turn the Pen so the plum-colored activator button is pointed up. See Figure G.

Figure G



- **Do not** press the plum-colored activator button until you are ready to inject HUMIRA. Pressing the plum-colored activator button will release the medicine from the Pen.
- Hold the Pen so that you can see the window. See Figure H. It is normal to see one or more bubbles in the window.

Figure H



Position the Pen and Inject HUMIRA

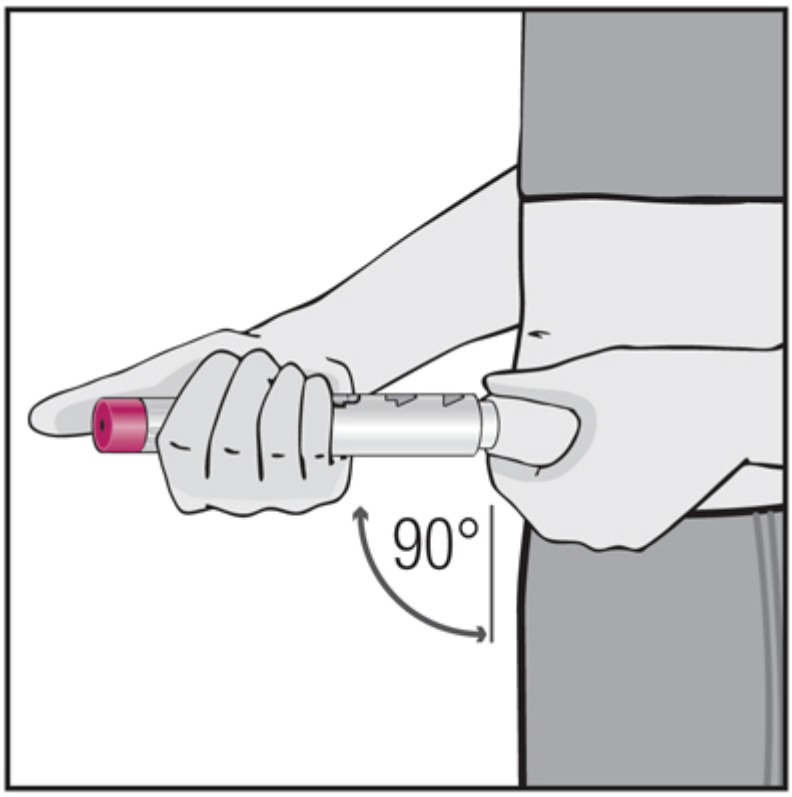
16. Position the Pen:
- Gently squeeze the area of the cleaned skin and hold it firmly. See Figure I. You will inject into this raised area of skin.

Figure I



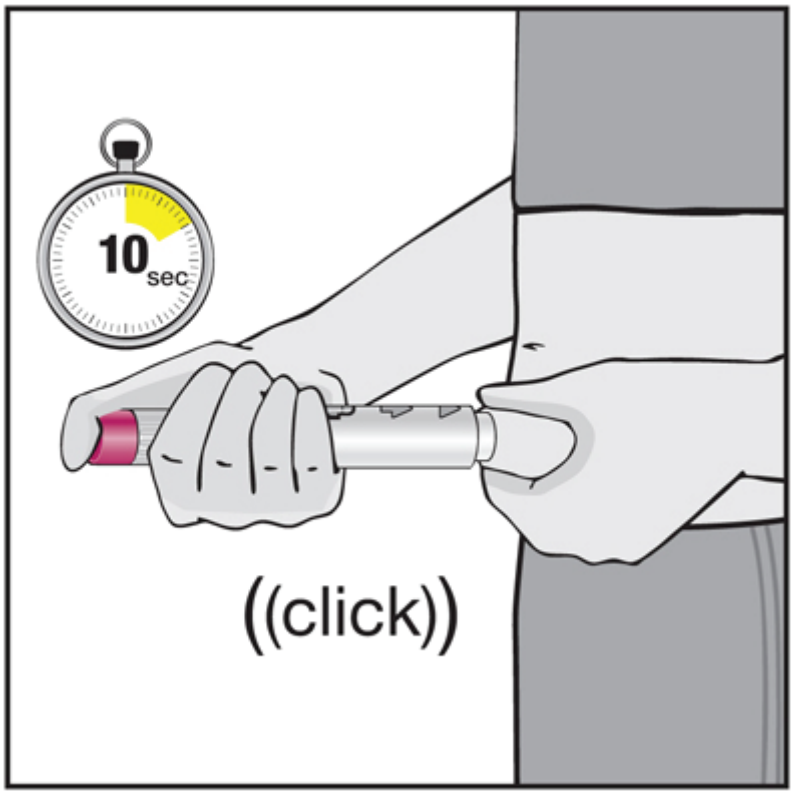
17. Place the white end of the Pen straight (at a 90º angle) and flat against the raised area of your skin that you are squeezing. Place the Pen so that it will not inject the needle into your fingers that are holding the raised skin. See Figure J.

Figure J



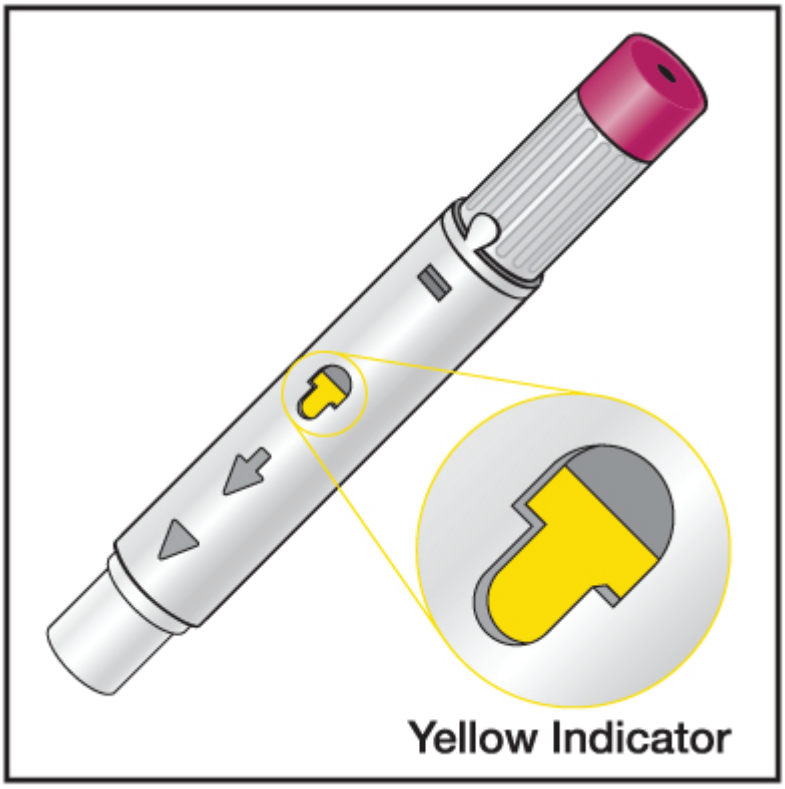
18. Inject HUMIRA
    - With your index finger or your thumb, press the plum-colored activator button to begin the injection. Try not to cover the window. See Figure K.

Figure K



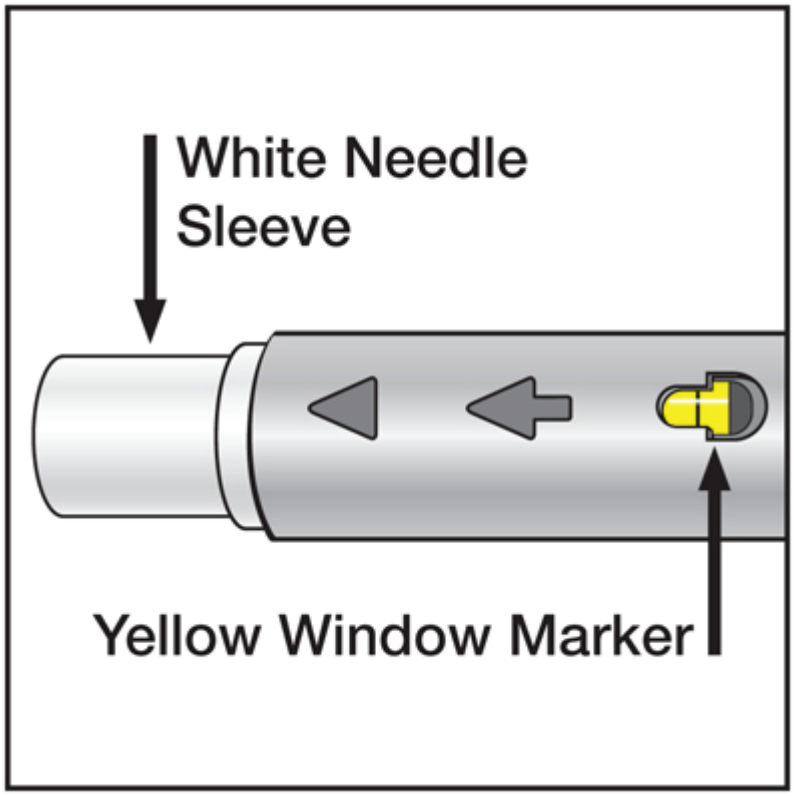
- You will hear a loud ‘click’ when you press the plum-colored activator button. The loud click means the start of the injection.
- Keep pressing the plum-colored activator button and continue to hold the Pen against your squeezed, raised skin until all of the medicine is injected. This can take up to 10 seconds, so count slowly to ten. Keep holding the Pen against the squeezed, raised skin of your injection site for the whole time so you get the full dose of medicine.
- You will know that the injection has finished when the yellow marker fully appears in the window view and stops moving. See Figure L.

Figure L



19. When the injection is finished, slowly pull the Pen from your skin. The white needle sleeve will move to cover the needle tip. See Figure M.
    - Do not touch the needle. The white needle sleeve is there to prevent you from touching the needle.

Figure M



- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

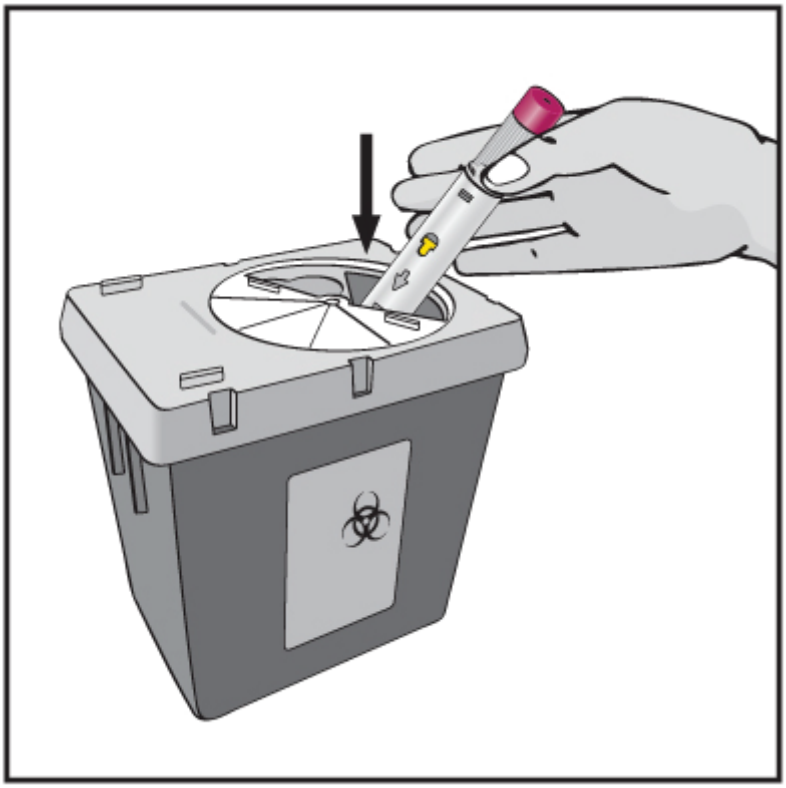
20. Dispose of your used HUMIRA Pen. See the section **"How should I dispose of the used HUMIRA Pen?"**

21. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of the used HUMIRA Pen?

- Put your Pen in a FDA-cleared sharps disposal container right away after use. See Figure N. **Do not throw away (dispose of) the Pen in your household trash.**
- Do not try to touch the needle. The white needle sleeve is there to prevent you from touching the needle.

Figure N



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- For the safety and health of you and others, never re-use your HUMIRA Pens.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

How should I store HUMIRA?

- Store HUMIRA in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Store HUMIRA in the original carton until use to protect it from light.
- **Do not** freeze HUMIRA. **Do not** use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray or Pen. **Do not** use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- Do not use a Pen if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA.
- Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

03-B355

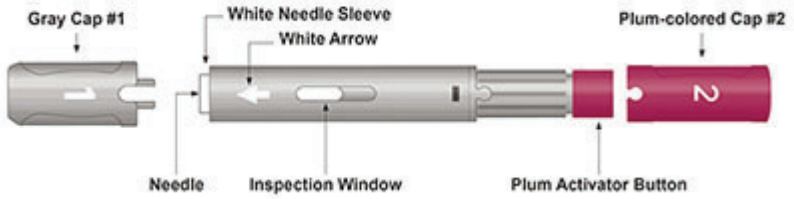
Revised: 06/2016

Instructions For Use

HUMIRA® (Hu-MARE-ah)
(adalimumab)
40 mg/0.4 mL
Single-Use Pen

Before Injecting: Your healthcare provider should show you how to use HUMIRA before you use it for the first time. Call your healthcare provider or **1-800-4HUMIRA** (1-800-448-6472) if you need help.

Figure A
HUMIRA Single-Use Pen



Do not use the Pen and call your healthcare provider or pharmacist if:

- Liquid is cloudy, discolored, or has flakes or particles in it
- Expiration date has passed
- Liquid has been frozen (even if thawed) or left in direct sunlight
- The Pen has been dropped or crushed

Keep the caps on until right before injection. Keep HUMIRA out of reach of children.

Read Instructions on All Pages Before Using the HUMIRA Pen



Take HUMIRA out of the refrigerator.
Leave HUMIRA at room temperature for **15 to 30 minutes** before injecting.

- **Do not** remove the Gray or Plum-colored Caps while allowing HUMIRA to reach room temperature
- **Do not** warm HUMIRA in any other way. For example, **do not** warm it in a microwave or in hot water.
- **Do not** use the Pen if liquid has been frozen (even if thawed)



Check expiration date on the Pen label. **Do not** use the Pen if expiration date has passed.
Place the following on a clean, flat surface:

- 1 single-use Pen and alcohol swab
- 1 cotton ball or gauze pad (not included)
- Puncture-resistant sharps disposal container (not included). See Step 9

Wash and dry your hands.

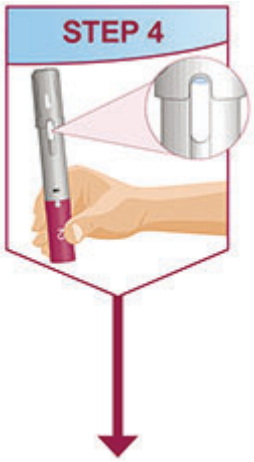


Choose an injection site:

- On the front of your thighs or
- Your abdomen (belly) at least 2 inches from your navel (belly button)
- Different from your last injection site

Wipe the injection site in a circular motion with the alcohol swab.

- **Do not** inject through clothes
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, has stretch marks, or areas with psoriasis plaques



Hold the Pen with the Gray Cap #1 facing up.
Check the window.

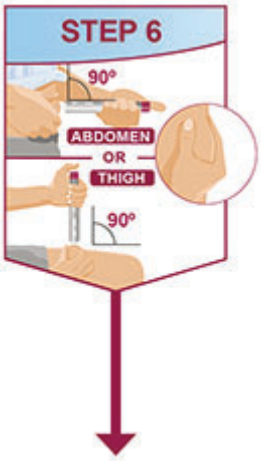
- It is normal to see 1 or more bubbles in the window
- Make sure the liquid is clear and colorless
- **Do not** use the Pen if the liquid is cloudy or has particles
- **Do not** use the Pen if it has been dropped or crushed



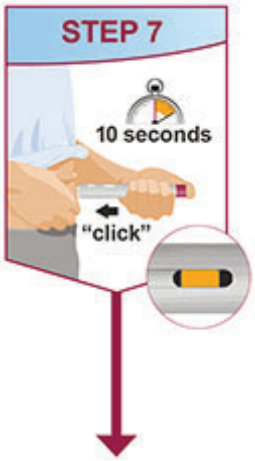
Pull the Gray Cap #1 straight off.
Throw the cap away.

- It is normal to see a few drops of liquid come out of the needle

Pull the Plum-colored Cap #2 straight off.
Throw the cap away.
Turn the Pen so that the white arrow points toward the injection site.



Squeeze the skin at your injection site to make a raised area and hold it firmly.
Point the white arrow toward the injection site.
Place the white needle sleeve straight **(90° angle)** against the injection site.
Hold the Pen so that you can see the inspection window.



Push and keep pushing the Pen **down** against the injection site.
Press the plum activator button and count slowly for **10** seconds.

- A loud "click" will signal the **start** of the injection
- **Keep pushing** the Pen **down** against the injection site
- Injection is complete when the yellow indicator has stopped moving



When the injection is completed, slowly pull the Pen from the skin. The white needle sleeve will cover the needle tip.
If there are more than a few drops of liquid on the injection site, call **1-800-4HUMIRA** (1-800-448-6472) for help.
After completing the injection, place a cotton ball or gauze pad on the skin of the injection site.

- **Do not** rub
- Slight bleeding at the injection site is normal



How should I dispose the used HUMIRA Pen?

- Put your used needles, Pens, and sharps in a FDA cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles, syringes, and the Pen in the household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

The Pen caps, alcohol swab, cotton ball or gauze pad, dose tray, and packaging may be placed in your household trash.

Questions About Using the HUMIRA Pen

What if I have not received in-person training from a healthcare provider?

- Call your healthcare provider or **1-800-4HUMIRA (1-800-448-6472)** or visit www.HUMIRA.com if you need help

How do I know when the injection is complete?

- The yellow indicator has stopped moving. This takes up to **10** seconds

What should I do if there are more than a few drops of liquid on the injection site?

- Call **1-800-4HUMIRA (1-800-448-6472)** for help

What if I do not have an FDA-cleared sharps disposal container or proper household container?

- Call **1-800-4HUMIRA (1-800-448-6472)** for a free FDA-cleared sharps disposal container



Always keep the Pen and the sharps disposal container out of reach of children.

Keep a record of the dates and locations of your injections. To help remember when to take HUMIRA, mark your calendar ahead of time.

abbvie

This Instructions For Use has been approved by the U.S. Food and Drug Administration.

Manufactured by AbbVie Inc. North Chicago, IL 60064 U.S.A.
US License Number 1889 03-B356 Revised 06/2016

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

40 MG/0.8 ML, 20 MG/0.4 ML AND 10 MG/0.2 ML

SINGLE-USE PREFILLED SYRINGE

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HUMIRA.

Gather the Supplies for Your Injection

- You will need the following supplies for each injection of HUMIRA.
  Find a clean, flat surface to place the supplies on.
  - 1 alcohol swab
  - 1 cotton ball or gauze pad (not included in your HUMIRA carton)
  - 1 HUMIRA prefilled syringe (See Figure A)
  - FDA-cleared sharps disposal container for HUMIRA prefilled syringe disposal (not included in your HUMIRA carton)

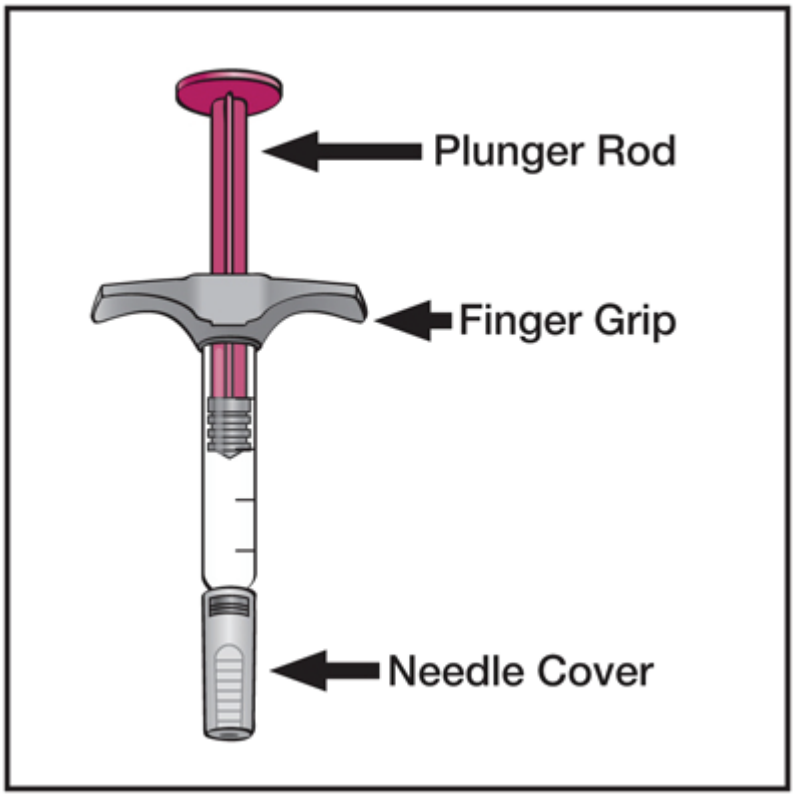
If more comfortable, take your HUMIRA prefilled syringe out of the refrigerator **15 to 30 minutes** before injecting to allow the liquid to reach room temperature. **Do not** remove the needle cover

while allowing it to reach room temperature. **Do not** warm HUMIRA in any other way (for example, **do not** warm it in a microwave or in hot water).

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist.

The diagram below shows what a prefilled syringe looks like. See Figure A.

Figure A



Check the carton, dose tray, and prefilled syringe

1. Make sure the name HUMIRA appears on the dose tray and prefilled syringe label.

2. **Do not use** and **do call** your doctor or pharmacist if:
   - the seals on top or bottom of the carton are broken or missing.
   - the HUMIRA labeling has an expired date. Check the expiration date on your HUMIRA carton and **do not** use if the date has passed.
   - the prefilled syringe that has been frozen or left in direct sunlight.
   - HUMIRA has been kept at room temperature for longer than **14** days or HUMIRA has been stored above 77°F (25°C).
   - the liquid in the prefilled syringe is cloudy, discolored or has flakes or particles in it. Make sure the liquid is clear and colorless.

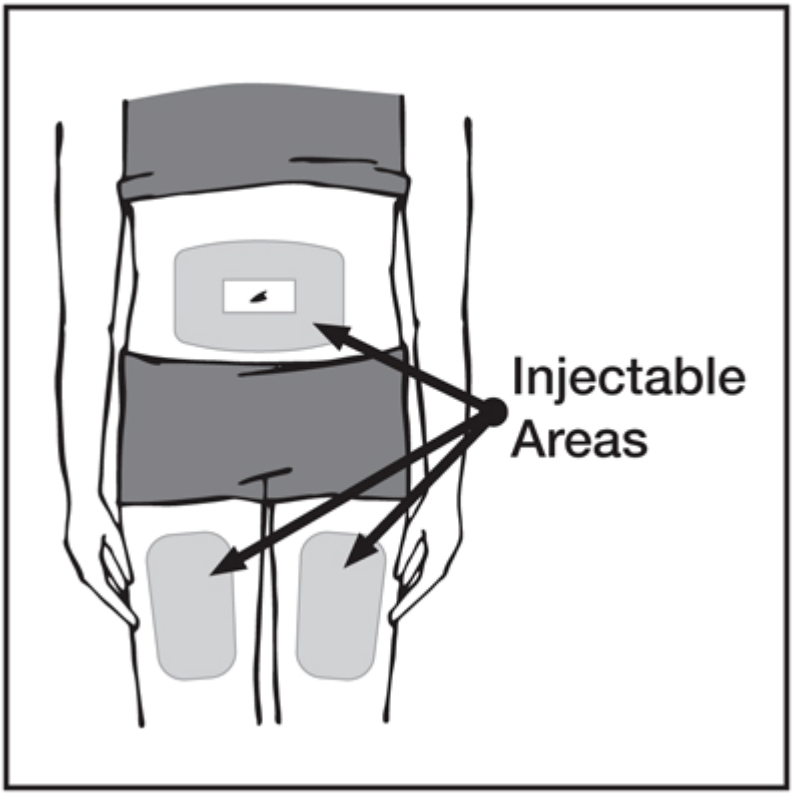
See the **"How should I store HUMIRA?"** section at the end of this Instructions for Use.

Choose the Injection Site

3. Wash and dry your hands well.

4. Choose an injection site on:
- the front of your thighs or
- your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure B.

Figure B



- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
- **Do not** inject into skin that is:
  - sore (tender)
  - bruised
  - red
  - hard
  - scarred or where you have stretch marks
- If you have psoriasis, do not inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

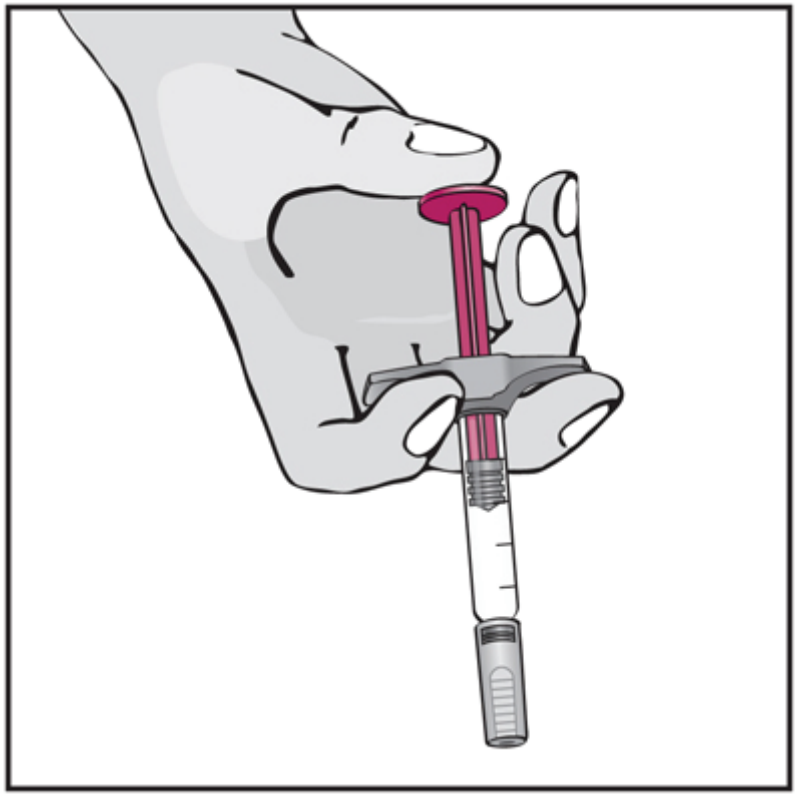
5. Wipe the injection site with an alcohol prep (swab) using a circular motion.

6. Do **not** touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Prepare the Syringe and Needle

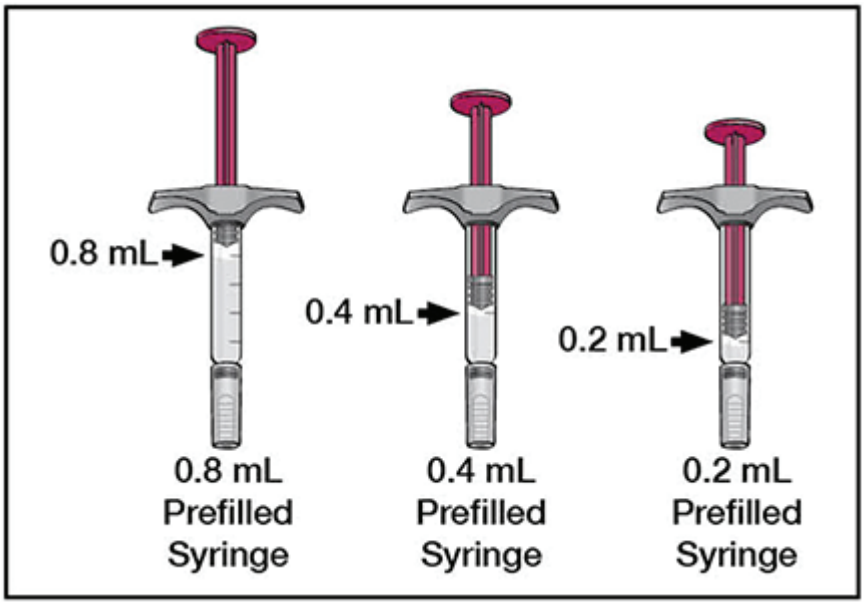
7. Check the fluid level in the syringe:
   - Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

Figure C



   - Hold the syringe at eye level. Look closely to make sure that the amount of liquid in the syringe is the same or close to the:
     - 0.8 mL line for the 40 mg prefilled syringe. See Figure D.
     - 0.4 mL line for the 20 mg prefilled syringe. See Figure D.
     - 0.2 mL line for the 10 mg prefilled syringe. See Figure D.

Figure D

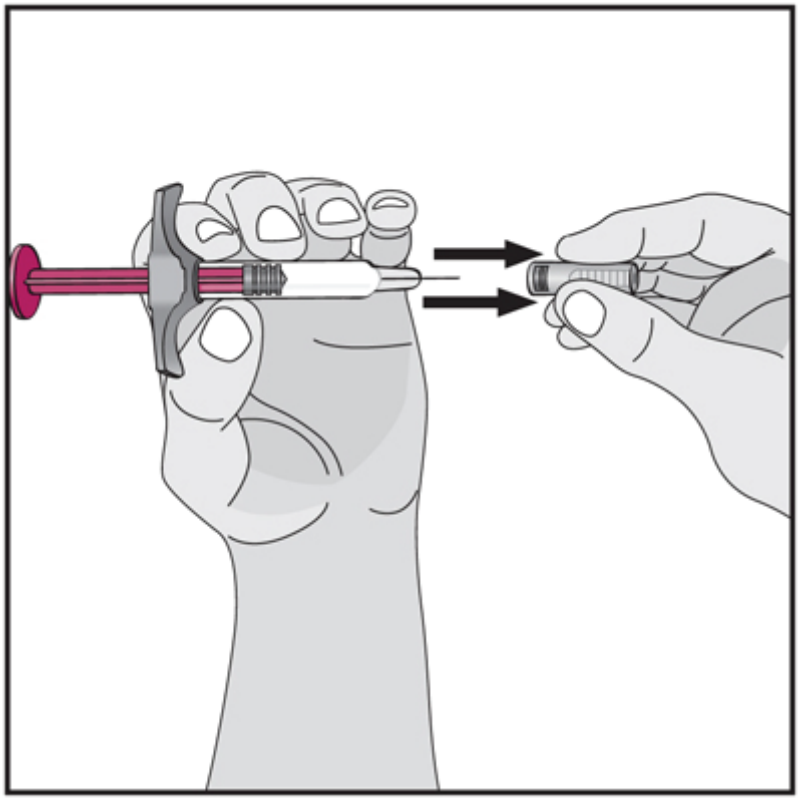


8. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.

9. Remove the needle cover:

- Hold the syringe in one hand. With the other hand gently remove the needle cover. See Figure E.
- Throw away the needle cover.

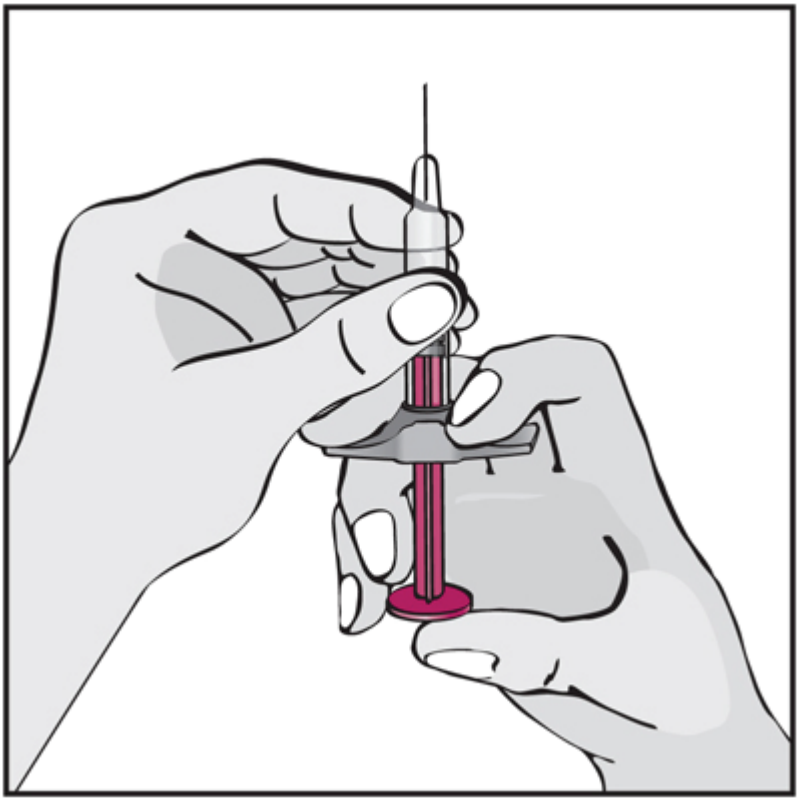
Figure E



- Do not touch the needle with your fingers or let the needle touch anything.

10. Turn the syringe so the needle is facing up and hold the syringe at eye level with one hand so you can see the air in the syringe. Using your other hand, slowly push the plunger in to push the air out through the needle. See Figure F.

Figure F



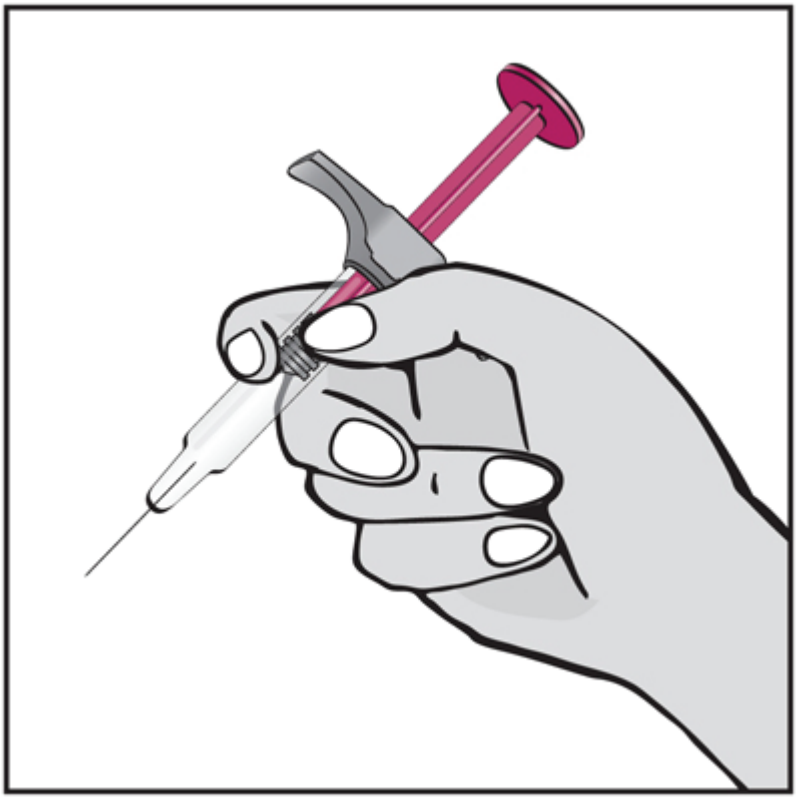
- You may see a drop of liquid at the end of the needle. This is normal.

Position the Prefilled Syringe and Inject HUMIRA

Position the Syringe

11. Hold the body of the prefilled syringe in one hand between the thumb and index finger. Hold the syringe in your hand like a pencil. See Figure G.

Figure G



- **Do not** pull back on the plunger at any time.
- With your other hand, gently squeeze the area of the cleaned skin and hold it firmly. See Figure H.

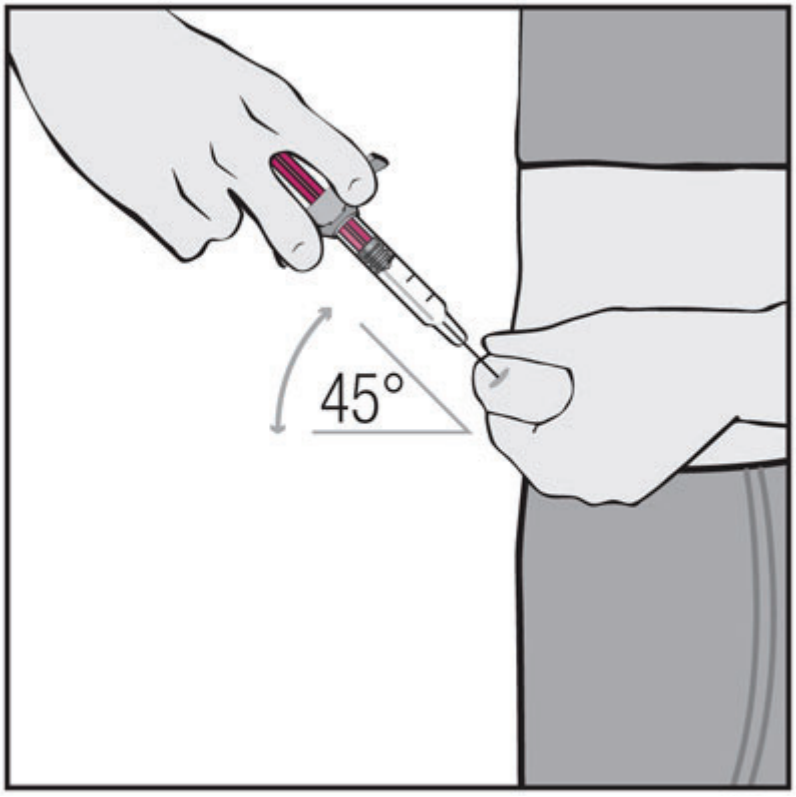
Figure H



Inject HUMIRA

12. Using a quick, dart-like motion, insert the needle into the squeezed skin at about a **45-degree angle**. See Figure I.

Figure I

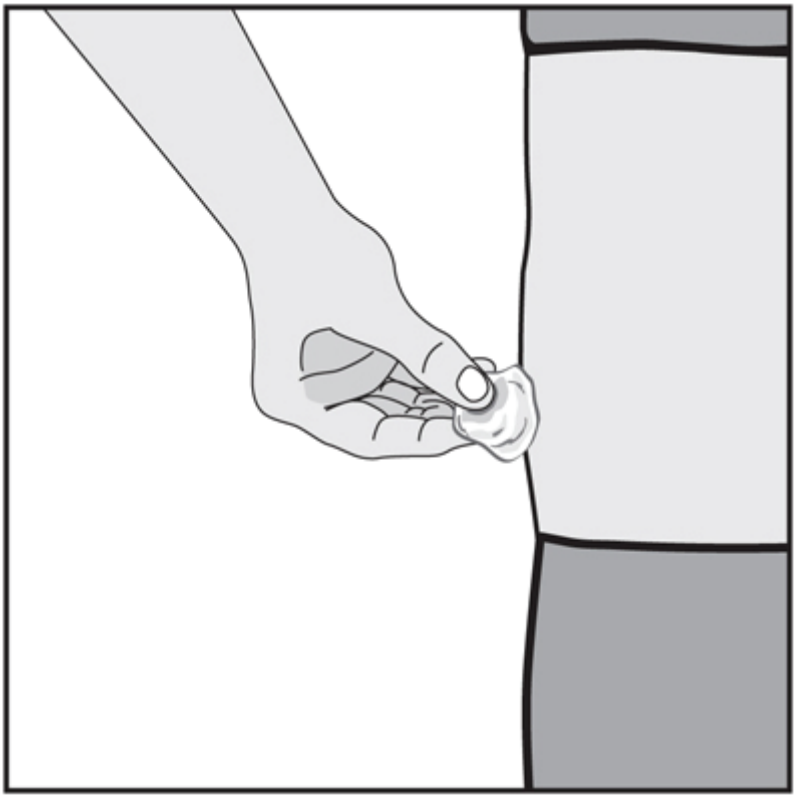


- After the needle is in, let go of the skin. Pull back gently on the plunger.

If blood appears in the syringe:

- It means that you have entered a blood vessel.
- **Do not inject HUMIRA.**
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. See Figure J.

Figure J



- **Do not** use the same syringe and needle again. Throw away the needle and syringe in your special sharps container.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.
- Repeat Steps 1 through 12 with a new prefilled syringe.

If no blood appears in the syringe:

- Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

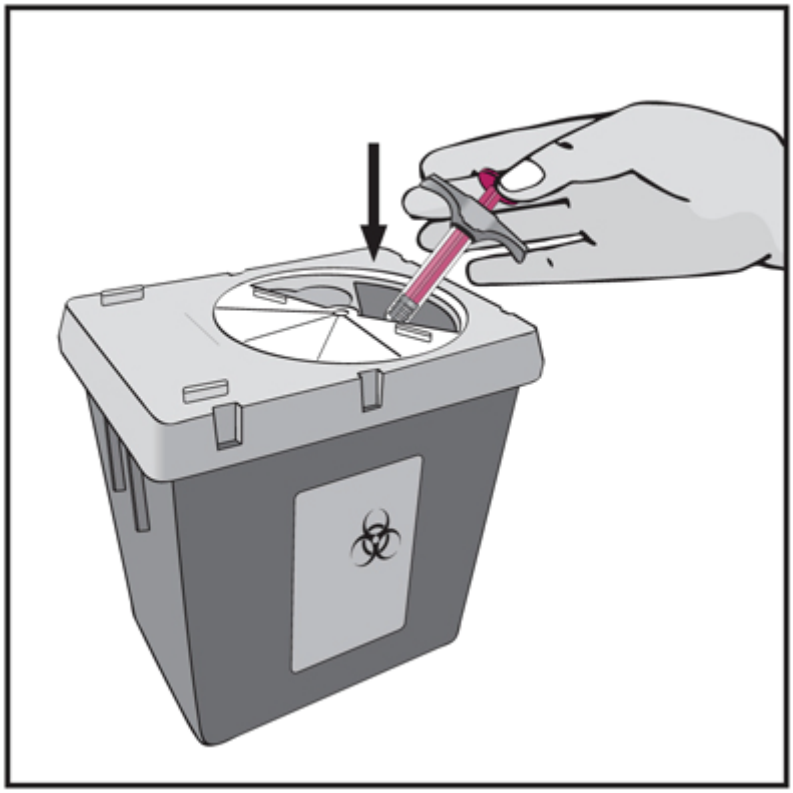
13. Throw away the used prefilled syringe and needle. See **"How should I dispose of used prefilled syringes and needles?"**

14. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of used prefilled syringes and needles?

- **Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use.** See Figure K. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- Do not try to touch the needle.

Figure K



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- For the safety and health of you and others, needles and used syringes **must never** be re-used.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

How should I store HUMIRA?

- Store HUMIRA in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Store HUMIRA in the original carton until use to protect it from light.
- **Do not** freeze HUMIRA. **Do not** use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray or prefilled syringe. **Do not** use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- Do not use a prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

03-B353

Revised: 06/2016

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

40 MG/0.4 ML

SINGLE-USE PREFILLED SYRINGE

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections and have read and understand this Instructions for Use. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. Call your healthcare provider if you or your caregiver have any questions about the right way to inject HUMIRA.

Gather the Supplies for Your Injection

- You will need the following supplies for each injection of HUMIRA.

  Find a clean, flat surface to place the supplies on.

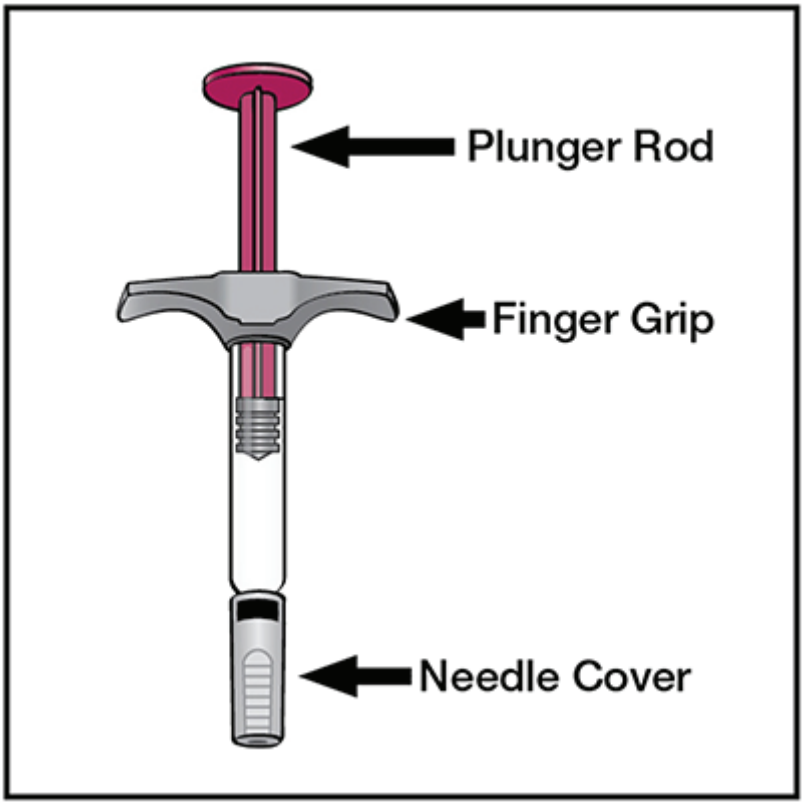
- 1 alcohol swab
- 1 cotton ball or gauze pad (not included in your HUMIRA carton)
- 1 HUMIRA prefilled syringe (See Figure A)
- FDA-cleared sharps disposal container for HUMIRA prefilled syringe disposal (not included in your HUMIRA carton)

If more comfortable, take your HUMIRA prefilled syringe out of the refrigerator **15 to 30 minutes** before injecting to allow the liquid to reach room temperature. **Do not** remove the needle cover while allowing it to reach room temperature. **Do not** warm HUMIRA in any other way (for example, **do not** warm it in a microwave or in hot water).

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist.

The diagram below shows what a prefilled syringe looks like. See Figure A.

Figure A



Check the carton, dose tray, and prefilled syringe

1. Make sure the name HUMIRA appears on the dose tray and prefilled syringe label.

2. **Do not use** and **do call** your doctor or pharmacist if:
   - the seals on top or bottom of the carton are broken or missing.
   - the HUMIRA labeling has an expired date. Check the expiration date on your HUMIRA carton and **do not use** if the date has passed.
   - the prefilled syringe that has been frozen or left in direct sunlight.

- HUMIRA has been kept at room temperature for longer than **14** days or HUMIRA has been stored above 77°F (25°C).
- the liquid in the prefilled syringe is cloudy, discolored or has flakes or particles in it. Make sure the liquid is clear and colorless.

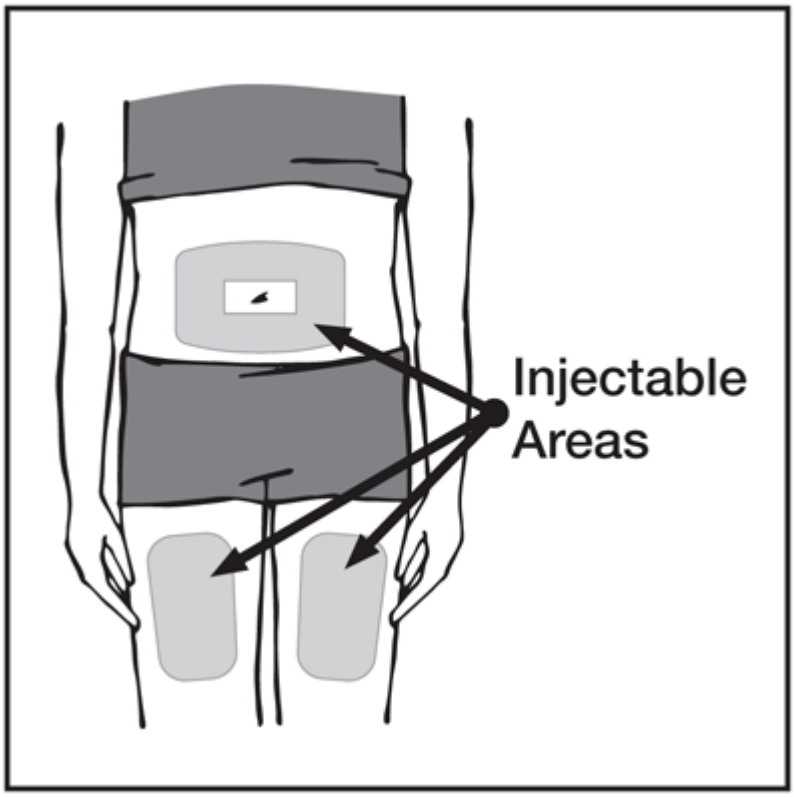
See the **"How should I store HUMIRA?"** section at the end of this Instructions for Use.

Choose the Injection Site

3. Wash and dry your hands well.

4. Choose an injection site on:
   - the front of your thighs or
   - your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure B.

Figure B



- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
- **Do not** inject into skin that is:
  - sore (tender)
  - bruised
  - red
  - hard
  - scarred or where you have stretch marks

- If you have psoriasis, do not inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

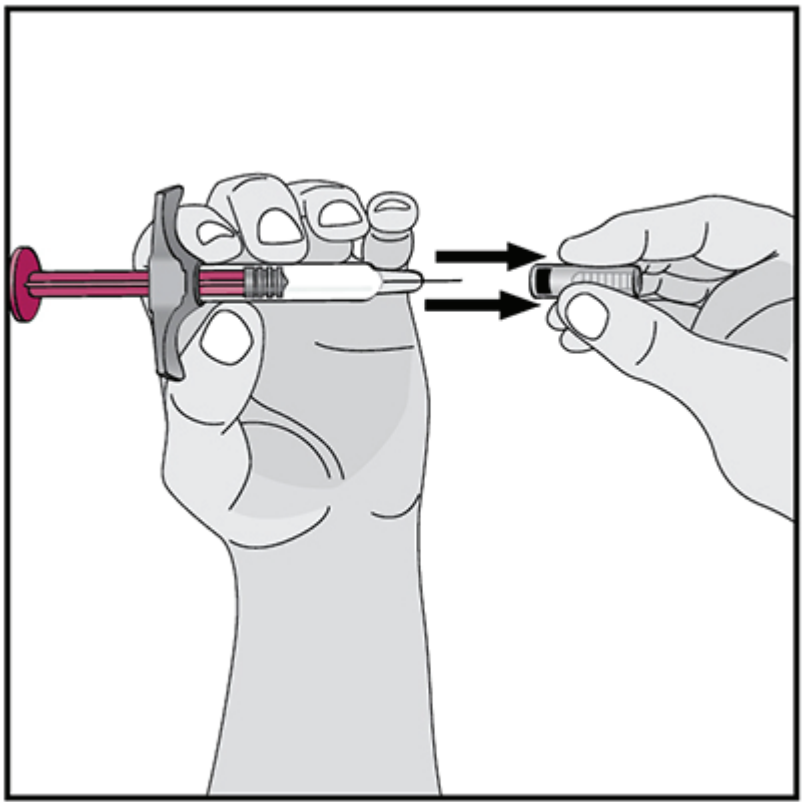
5. Wipe the injection site with an alcohol prep (swab) using a circular motion.

6. Do **not** touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Prepare the Syringe and Needle

7. Remove the needle cover:
- Always hold the prefilled syringe by the body of the syringe.
- Hold the syringe in one hand. With the other hand gently remove the needle cover. See Figure C.
- Throw away the needle cover.

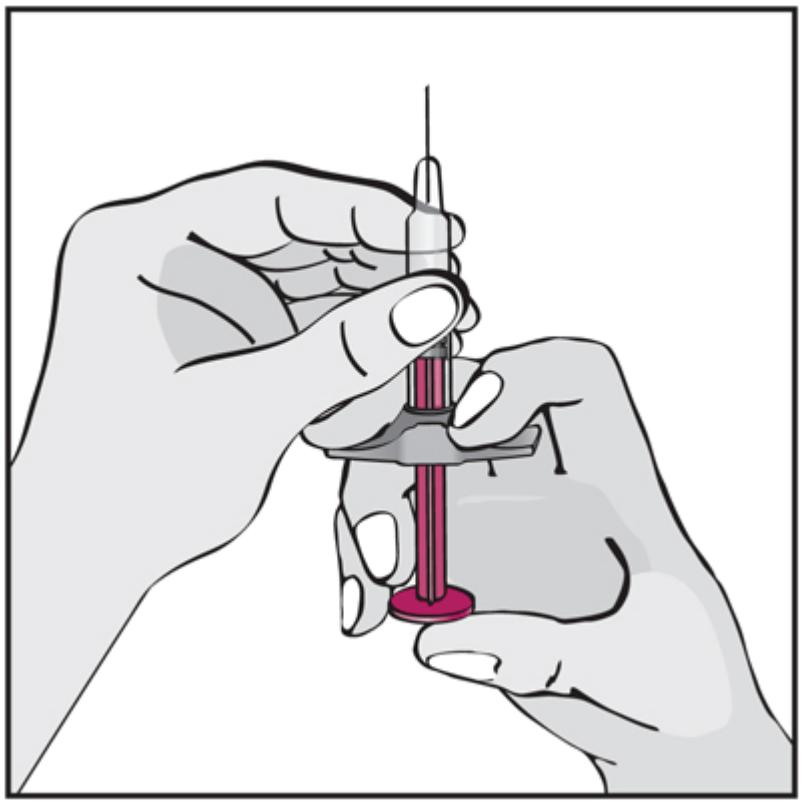
Figure C



- Do not touch the needle with your fingers or let the needle touch anything.

8. Turn the syringe so the needle is facing up and hold the syringe at eye level with one hand so you can see the air in the syringe. Using your other hand, slowly push the plunger in to push the air out through the needle. See Figure D.

Figure D



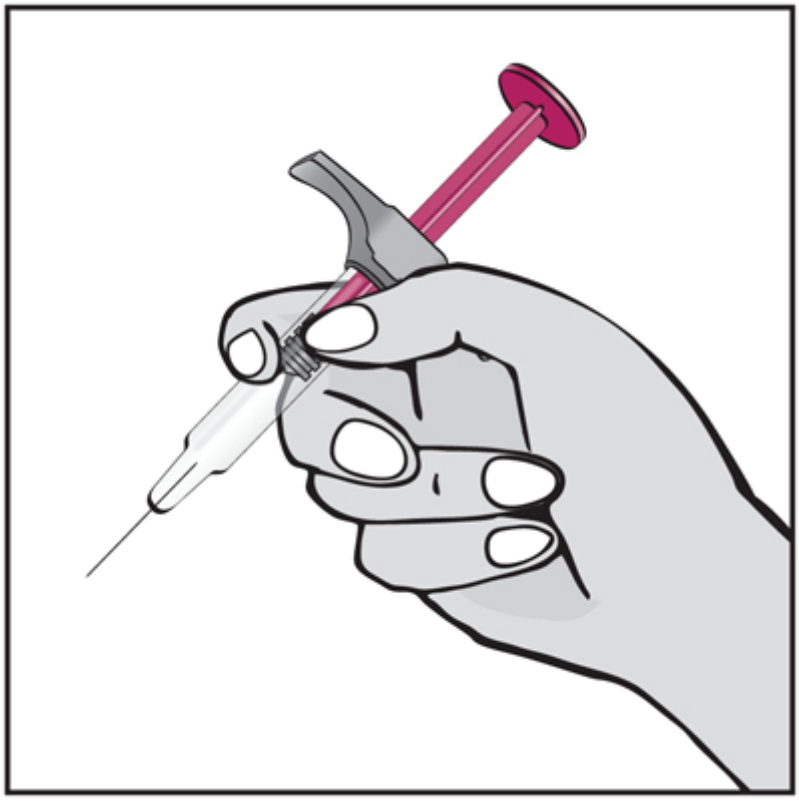
- You may see a drop of liquid at the end of the needle. This is normal.

Position the Prefilled Syringe and Inject HUMIRA

Position the Syringe

9. Hold the body of the prefilled syringe in one hand between the thumb and index finger. Hold the syringe in your hand like a pencil. See Figure E.

Figure E



- **Do not** pull back on the plunger at any time.
- With your other hand, gently squeeze the area of the cleaned skin and hold it firmly. See Figure F.

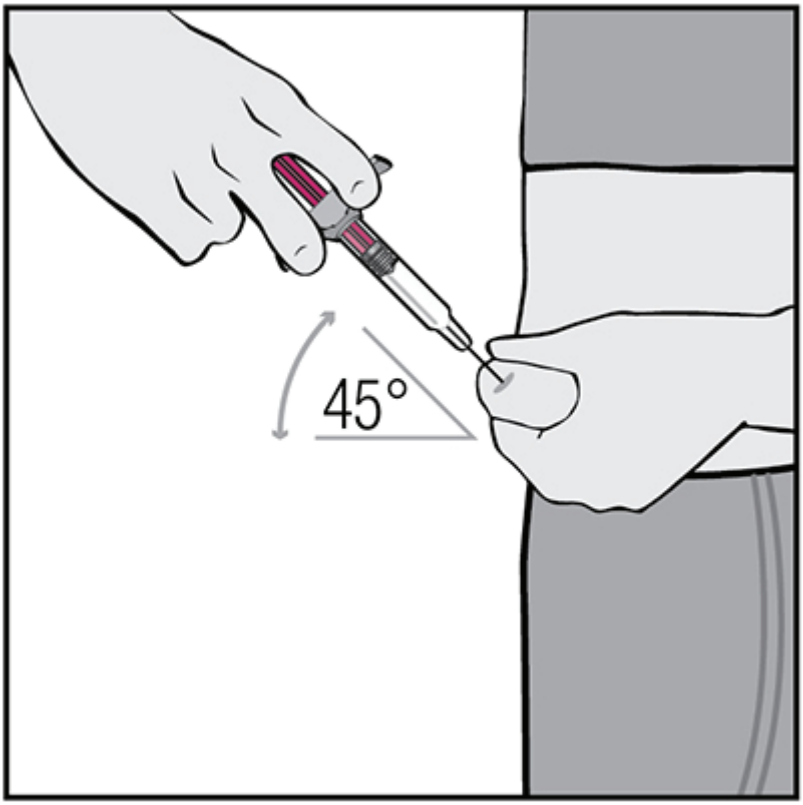
Figure F



Inject HUMIRA

10. Using a quick, dart-like motion, insert the needle into the squeezed skin at about a **45-degree angle**. See Figure G.

Figure G

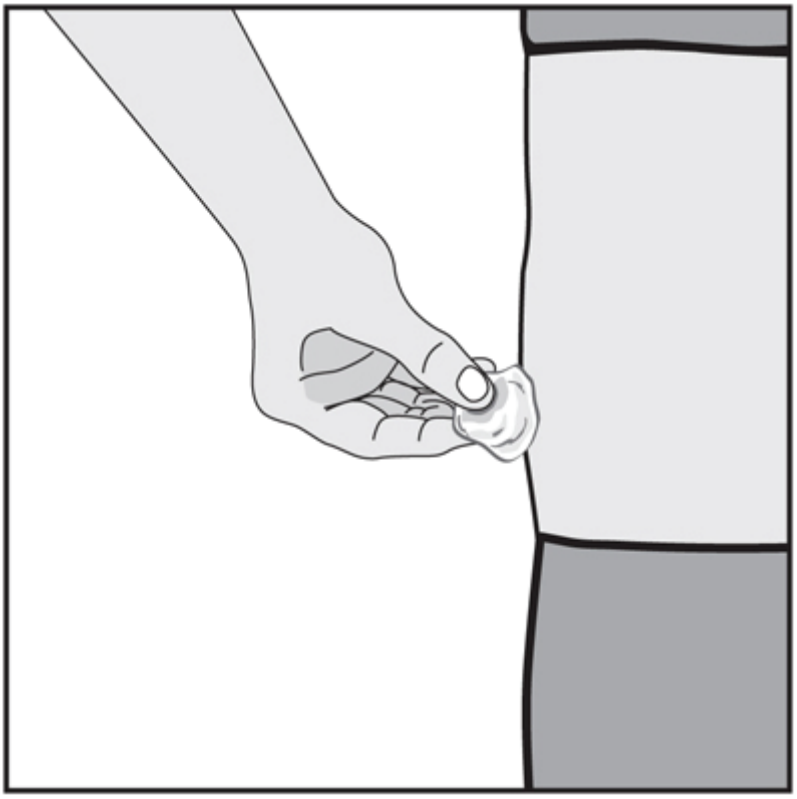


- After the needle is in, let go of the skin. Pull back gently on the plunger.

If blood appears in the syringe:

- It means that you have entered a blood vessel.
- **Do not inject HUMIRA.**
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. See Figure H.

Figure H



- **Do not** use the same syringe and needle again. Throw away the needle and syringe in your special sharps container.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.
- Repeat Steps 1 through 10 with a new prefilled syringe.

If no blood appears in the syringe:

- Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

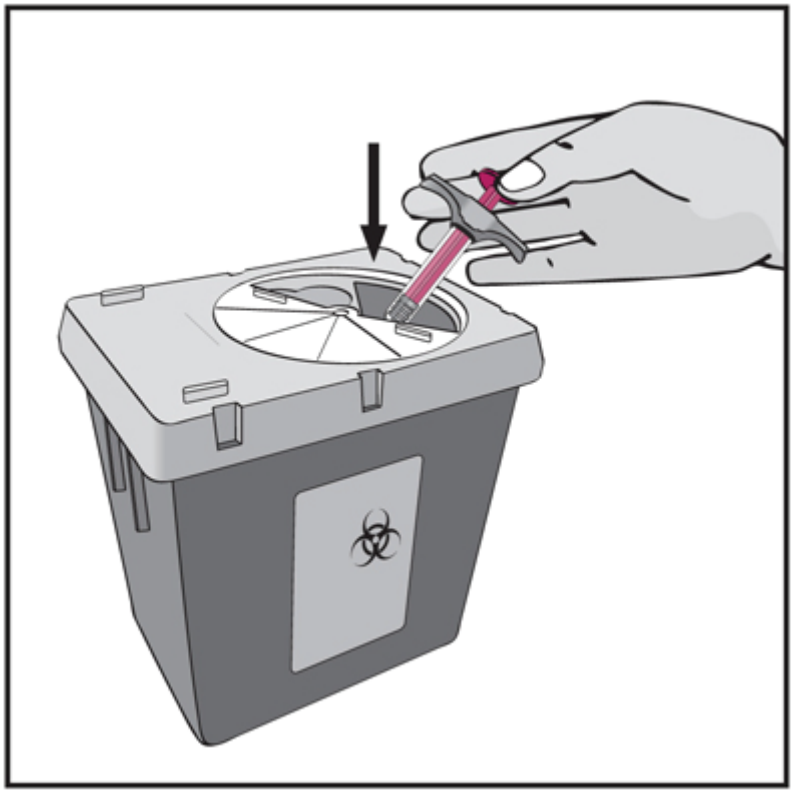
11. Throw away the used prefilled syringe and needle. See **"How should I dispose of used prefilled syringes and needles?"**

12. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of used prefilled syringes and needles?

- **Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use.** See Figure I. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- Do not try to touch the needle.

Figure I



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- For the safety and health of you and others, needles and used syringes **must never** be re-used.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

How should I store HUMIRA?

- Store HUMIRA in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Store HUMIRA in the original carton until use to protect it from light.
- **Do not** freeze HUMIRA. **Do not** use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray or prefilled syringe. **Do not** use HUMIRA after the expiration date.
- If needed, for example when you are traveling, you may also store HUMIRA at room temperature up to 77°F (25°C) for up to **14** days. Store HUMIRA in the original carton until use to protect it from light.
- Throw away HUMIRA if it has been kept at room temperature and not been used within **14** days.
- Record the date you first remove HUMIRA from the refrigerator in the spaces provided on the carton and dose tray.
- Do not store HUMIRA in extreme heat or cold.
- Do not use a prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

03-B354

Revised: 06/2016

https://web.archive.org/web/20170712144306/https://www.stelarainfo.com/pdf/prescribinginformation.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STELARA® safely and effectively. See full prescribing information for STELARA®.

STELARA® (ustekinumab) injection, for subcutaneous or intravenous use

Initial U.S. Approval: 2009

---------- RECENT MAJOR CHANGES ----------

Indications and Usage, Crohn's Disease (1.3)	09/2016
Dosage and Administration (2.3)	09/2016
Dosage and Administration (2.6)	09/2016

---------- INDICATIONS AND USAGE ----------

STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of adult patients with:

- *moderate to severe plaque psoriasis (Ps)* who are candidates for phototherapy or systemic therapy. (1.1)
- *active psoriatic arthritis (PsA)*, alone or in combination with methotrexate. (1.2)
- *moderately to severely active Crohn's disease (CD)* who have
  - failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker or
  - failed or were intolerant to treatment with one or more TNF blockers. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

Psoriasis Recommended Adult Subcutaneous Dosage (2.1):

Weight Range (kilogram)	Dosage Regimen
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks

Psoriatic Arthritis Recommended Adult Subcutaneous Dosage (2.2):

- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Crohn's Disease Recommended Initial Adult Intravenous Dosage (2.3):

A single intravenous infusion using weight-based dosing:

Weight Range (kilogram)	Recommended Dosage
Up to 55 kg	260 mg (2 vials)
Greater than 55 kg to 85 kg	390 mg (3 vials)
Greater than 85 kg	520 mg (4 vials)

Crohn's Disease Recommended Maintenance Adult Subcutaneous Dosage (2.3):

A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

---------- DOSAGE FORMS AND STRENGTHS ----------

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL in a single-dose prefilled syringe (3)
- Injection: 45 mg/0.5 mL in a single-dose vial (3)

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial (3)

---------- CONTRAINDICATIONS ----------

Clinically significant hypersensitivity to ustekinumab or to any of the excipients. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing STELARA® until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STELARA®. Initiate treatment of latent TB before administering STELARA®. (5.3)
- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur. (5.5)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA®. (5.6)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions are:

- Psoriasis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)
- Crohn's Disease, induction (≥3%): vomiting. (6.1)
- Crohn's Disease, maintenance (≥3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Psoriasis (Ps)

STELARA® is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

STELARA® is indicated for the treatment of adult patients with active psoriatic arthritis. STELARA® can be used alone or in combination with methotrexate (MTX).

1.3 Crohn's Disease

STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have:

- failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker or
- failed or were intolerant to treatment with one or more TNF blockers.

2 DOSAGE AND ADMINISTRATION

2.1 Psoriasis

Subcutaneous Adult Dosage Regimen

- For patients weighing 100 kg or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

In subjects weighing more than 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects *[see Clinical Studies (14)]*.

2.2 Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

2.3 Crohn's Disease

Intravenous Induction Adult Dosage Regimen

A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 1 *[see Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)]*.

Table 1: Initial Intravenous Dosage of STELARA®

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4

Subcutaneous Maintenance Adult Dosage Regimen

The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

2.4 General Considerations for Administration

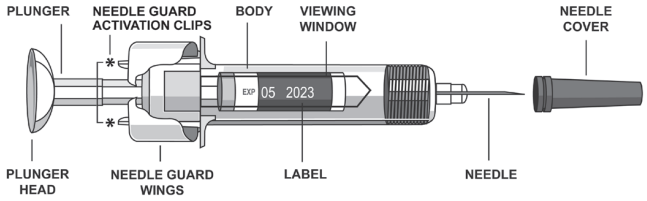
- After proper training in subcutaneous injection technique, a patient may self-inject with STELARA® if a physician determines that it is appropriate. Patients should be instructed to follow the directions provided in the Medication Guide *[see Medication Guide]*.
- The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The needle cover should not be handled by persons sensitive to latex.
- It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated. When using the single-dose vial, a 27 gauge, ½ inch needle is recommended.
- STELARA® is intended for use under the guidance and supervision of a physician. STELARA® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.
- Prior to administration, visually inspect STELARA® for particulate matter and discoloration. STELARA® is clear, colorless to light yellow and may contain a few small translucent or white particles. Do not use STELARA® if it is discolored or cloudy, or if other particulate matter is present. STELARA® does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

STELARA® (ustekinumab)

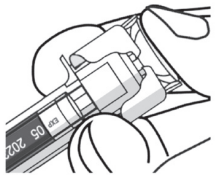
2.5 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard

Refer to the diagram below for the provided instructions.

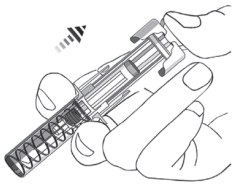
To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.



- Hold the BODY and remove the NEEDLE COVER. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE COVER or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE COVER in place.**
- Inject STELARA® subcutaneously as recommended *[see Dosage and Administration (2.1, 2.2, 2.3)]*.
- Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the needle guard wings. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard.**



- After injection, maintain the pressure on the PLUNGER HEAD and remove the needle from the skin. Slowly take your thumb off the PLUNGER HEAD to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by the illustration below:



- Used syringes should be placed in a puncture-resistant container.

2.6 Preparation and Administration of STELARA® 130 mg/26 mL (5 mg/mL) Vial for Intravenous Infusion (Crohn's Disease)

STELARA® solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA® vials needed based on patient weight (Table 1). Each 26 mL vial of STELARA® contains 130 mg of ustekinumab.
2. Withdraw, and then discard a volume of the 0.9% Sodium Chloride Injection, USP from the 250 mL infusion bag equal to the volume of STELARA® to be added (discard 26 mL sodium chloride for each vial of STELARA® needed, for 2 vials- discard 52 mL, for 3 vials- discard 78 mL, 4 vials- discard 104 mL).
3. Withdraw 26 mL of STELARA® from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion solution may be stored for up to four hours prior to infusion.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Do not infuse STELARA® concomitantly in the same intravenous line with other agents.
8. STELARA® does not contain preservatives. Each vial is for single use only. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be stored for up to 4 hours at room temperature up to 25°C (77°F). Do not freeze. Discard any unused portion of the infusion solution.

3 DOSAGE FORMS AND STRENGTHS

STELARA® (ustekinumab) is colorless to slightly yellow solution.

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL in a single-dose vial

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

STELARA® is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

STELARA® may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in subjects receiving STELARA® *[see Adverse Reactions (6.1)]*.

Serious infections requiring hospitalization occurred in patients with psoriasis, psoriatic arthritis and Crohn's disease in clinical studies. In patients with psoriasis, serious infections included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections. In patients with psoriatic arthritis, serious infections included cholecystitis. In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, ophthalmic herpes, pneumonia, and listeria meningitis.

Treatment with STELARA® should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STELARA® in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with STELARA® and consider discontinuing STELARA® for serious or clinically significant infections until the infection resolves or is adequately treated.

5.2 Theoretical Risk for Vulnerability to Particular Infections

Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances.

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis infection prior to initiating treatment with STELARA®.

Do not administer STELARA® to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering STELARA®. Consider anti-tuberculosis therapy prior to initiation of STELARA® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving STELARA® for signs and symptoms of active tuberculosis during and after treatment.

5.4 Malignancies

STELARA® is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA® in clinical studies *[see Adverse Reactions (6.1)]*. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy *[see Nonclinical Toxicology (13)]*.

The safety of STELARA® has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

There have been post marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving STELARA® who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving STELARA® should be monitored for the appearance of non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely *[see Adverse Reactions (6.1)]*.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with STELARA® *[see Adverse Reactions (6.1, 6.3)]*. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®.

5.6 Reversible Posterior Leukoencephalopathy Syndrome

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed in clinical studies of psoriasis and psoriatic arthritis. The subject, who had received 12 doses of STELARA® over approximately two years, presented with headache, seizures and confusion. No additional STELARA® injections were administered and the subject fully recovered with appropriate treatment. No cases of RPLS were observed in clinical studies of Crohn's disease.

STELARA® (ustekinumab)

RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported.

If RPLS is suspected, administer appropriate treatment and discontinue STELARA®.

5.7 Immunizations

Prior to initiating therapy with STELARA®, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with STELARA® should not receive live vaccines. BCG vaccines should not be given during treatment with STELARA® or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving STELARA® because of the potential risk for shedding from the household contact and transmission to patient.

Non-live vaccinations received during a course of STELARA® may not elicit an immune response sufficient to prevent disease.

5.8 Concomitant Therapies

In clinical studies of psoriasis the safety of STELARA® in combination with other immunosuppressive agents or phototherapy was not evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone *[see Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Psoriasis

The safety data reflect exposure to STELARA® in 3117 psoriasis subjects, including 2414 exposed for at least 6 months, 1855 exposed for at least one year, 1653 exposed for at least two years, 1569 exposed for at least three years, 1482 exposed for at least four years and 838 exposed for at least five years.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the STELARA® groups than the placebo group during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14)]*.

Table 2: Adverse reactions reported by ≥1% of subjects through Week 12 in Ps STUDY 1 and Ps STUDY 2

		STELARA®	
	Placebo	45 mg	90 mg
Subjects treated	**665**	**664**	**666**
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

Adverse reactions that occurred at rates less than 1% in the controlled period of Ps STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

One case of RPLS occurred during clinical studies *[see Warnings and Precautions (5.6)]*.

Infections

In the placebo-controlled period of clinical studies of psoriasis subjects (average follow-up of 12.6 weeks for placebo-treated subjects and 13.4 weeks for STELARA®-treated subjects), 27% of STELARA®-treated subjects reported infections (1.39 per subject-year of follow-up) compared with 24% of placebo-treated subjects (1.21 per subject-year of follow-up). Serious infections occurred in 0.3% of STELARA®-treated subjects (0.01 per subject-year of follow-up) and in 0.4% of placebo-treated subjects (0.02 per subject-year of follow-up) *[see Warnings and Precautions (5.1)]*.

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In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years), representing 8998 subject-years of exposure, 72.3% of STELARA®-treated subjects reported infections (0.87 per subject-years of follow-up). Serious infections were reported in 2.8% of subjects (0.01 per subject-years of follow-up).

Malignancies

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years, representing 8998 subject-years of exposure), 1.7% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of STELARA®-treated subjects (0.52 per hundred subject-years of follow-up) *[see Warnings and Precautions (5.4)]*. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical studies were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in STELARA®-treated patients during the controlled and uncontrolled portions of studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender and race).[1]

Psoriatic Arthritis

The safety of STELARA® was assessed in 927 patients in two randomized, double-blind, placebo-controlled studies in adult patients with active psoriatic arthritis (PsA). The overall safety profile of STELARA® in patients with PsA was consistent with the safety profile seen in psoriasis clinical studies. A higher incidence of arthralgia, nausea, and dental infections was observed in STELARA®-treated patients when compared with placebo-treated patients (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo-controlled portions of the PsA clinical studies.

Crohn's Disease

The safety of STELARA® was assessed in 1407 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter studies. These 1407 patients included 40 patients who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In Studies CD-1 and CD-2 there were 470 patients who received STELARA® 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3)]*. Patients who were responders in either Study CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or placebo for 44 weeks in Study CD-3. Patients in these 3 studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX)], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's Disease *[see Clinical Studies (14.3)]*.

The overall safety profile of STELARA® was consistent with the safety profile seen in the psoriasis and psoriatic arthritis clinical studies. Common adverse reactions in Studies CD-1 and CD-2 and in Study CD-3 are listed in Tables 3 and 4, respectively.

Table 3: Common adverse reactions through Week 8 in Studies CD-1 and CD-2 occurring in ≥3% of STELARA®-treated patients and higher than placebo

	Placebo N=466	STELARA® 6 mg/kg single intravenous induction dose N=470
Vomiting	3%	4%

Other less common adverse reactions reported in patients in Studies CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 4: Common adverse reactions through Week 44 in Study CD-3 occurring in ≥3% of STELARA®-treated patients and higher than placebo

	Placebo N=133	STELARA® 90 mg subcutaneous maintenance dose every 8 weeks N=131
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

STELARA® (ustekinumab)

Infections

In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes were reported in one patient each.

Malignancies

With up to one year of treatment in the Crohn's disease clinical studies, 0.2% of STELARA®-treated patients (0.36 events per hundred patient-years) and 0.2% of placebo-treated patients (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.2% of STELARA®-treated patients (0.27 events per hundred patient-years) and in none of the placebo-treated patients.

Hypersensitivity Reactions Including Anaphylaxis

In CD studies, two patients reported hypersensitivity reactions following STELARA® administration. One patient experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of patients receiving subcutaneous STELARA®). In addition, one patient experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous STELARA® dose (0.08% of patients receiving intravenous STELARA®). These patients were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour.

6.2 Immunogenicity

Approximately 6% of patients treated with STELARA® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titer. In Crohn's disease clinical studies, less than 3% of patients treated with STELARA® developed antibodies to ustekinumab. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen. No ustekinumab-related serious hypersensitivity reactions were observed in psoriasis, psoriatic arthritis and Crohn's disease clinical studies. In psoriasis studies, the majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

The data above reflect the percentage of subjects whose test results were positive for antibodies to ustekinumab and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ustekinumab with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval of STELARA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to STELARA® exposure.

Immune system disorders: Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria) *[see Warnings and Precautions (5.5)]*.

Skin reactions: Pustular psoriasis, erythrodermic psoriasis.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines with STELARA® *[see Warnings and Precautions (5.7)]*.

7.2 Concomitant Therapies

In psoriasis studies the safety of STELARA® in combination with immunosuppressive agents or phototherapy has not been evaluated *[see Warnings and Precautions (5.8)]*. In psoriatic arthritis studies, concomitant methotrexate use did not appear to influence the safety or efficacy of STELARA®. In Crohn's disease studies, immunomodulators (6-mercaptopurine, azathioprine, methotrexate) were used concomitantly in approximately 30% of patients and corticosteroids were used concomitantly in approximately 40% of patients. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of STELARA®.

7.3 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, STELARA®, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA® in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed *[see Clinical Pharmacology (12.3)]*.

7.4 Allergen Immunotherapy

STELARA® has not been evaluated in patients who have undergone allergy immunotherapy. STELARA® may decrease the protective effect of allergen immunotherapy (decrease tolerance) which may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergen immunotherapy, particularly for anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to STELARA® during pregnancy. Patients should be encouraged to enroll by calling 1-877-311-8972.

Risk Summary

Limited data on the use of STELARA® in pregnant women are insufficient to inform a drug associated risk *[see Data]*. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the human exposure at the maximum recommended human subcutaneous dose (MRHD).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Limited data on use of STELARA® in pregnant women from observational studies, published case reports, and postmarketing surveillance are insufficient to inform a drug associated risk.

Animal Data

Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks.

In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly at exposures greater than 100 times the human subcutaneous exposure from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab-related effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of ustekinumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ustekinumab was present in the milk of lactating monkeys administered ustekinumab. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Maternal IgG is known to be present in human milk. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule and is degraded in the gastrointestinal tract. However, if ustekinumab is transferred into human milk the effects of local exposure in the gastrointestinal tract are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STELARA® and any potential adverse effects on the breastfed child from STELARA® or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of STELARA® in pediatric patients have not been established.

8.5 Geriatric Use

Of the 5884 subjects exposed to STELARA®, a total of 306 were 65 years or older (183 patients with psoriasis, 65 patients with psoriatic arthritis and 58 with Crohn's disease), and 34 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

Single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, ustekinumab is produced in a well characterized recombinant cell line and is purified using standard bio-processing technology. The manufacturing process contains steps for the clearance of viruses. Ustekinumab is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

STELARA® (ustekinumab)

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to slightly yellow solution that may contain a few small translucent or white particles with pH of 5.7- 6.3.

STELARA® for Subcutaneous Use

Available as 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL, supplied as a sterile solution in a single-dose prefilled syringe with a 27 gauge fixed ½ inch needle and as 45 mg of ustekinumab in 0.5 mL in a single-dose 2 mL Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cover that contains dry natural rubber (a derivative of latex).

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

STELARA® for Intravenous Infusion

Available as 130 mg of ustekinumab in 26 mL, supplied as a single-dose 30 mL Type I glass vial with a coated stopper.

Each 26 mL vial delivers 130 mg ustekinumab, EDTA disodium salt dihydrate (0.52 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's Disease. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

12.2 Pharmacodynamics

In a small exploratory study, a decrease was observed in the expression of mRNA of its molecular targets IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to two weeks post-treatment in subjects with psoriasis.

12.3 Pharmacokinetics

Absorption

In subjects with psoriasis, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in subjects with psoriasis.

Following multiple subcutaneous doses of STELARA® in patients with psoriasis, the steady-state serum concentrations of ustekinumab were achieved by Week 28. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease, following the recommended intravenous induction dose, mean peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL. Starting at Week 8, the recommended subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in ustekinumab concentration over time when given subcutaneously every 8 weeks. Mean steady-state trough concentration was 2.51 ± 2.06 mcg/mL for 90 mg ustekinumab administered every 8 weeks.

Distribution

In a population pharmacokinetic analysis of ustekinumab, the volume of distribution of the central compartment was 2.74 L (95% CI: 2.69, 2.78), and the total volume of distribution at steady-state was 4.62 L in patients with Crohn's disease.

Elimination

The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following subcutaneous administration. In a population pharmacokinetic analysis of ustekinumab, the clearance was 0.19 L/day (95% CI: 0.185, 0.197) with an estimated median terminal half-life of approximately 19 days in patients with Crohn's disease.

Metabolism

The metabolic pathway of ustekinumab has not been characterized. As a human IgG1κ monoclonal antibody ustekinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Specific Populations

Weight

When given the same dose, subjects with psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of higher weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group.

Age: Geriatric Population

A population pharmacokinetic analysis (N=106/1937 patients with psoriasis greater than or equal to 65 years old) was performed to evaluate the effect of age on the pharmacokinetics of ustekinumab. There were no apparent changes in pharmacokinetic parameters (clearance and volume of distribution) in subjects older than 65 years old.

Drug Interaction Studies

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). However, the clinical relevance of *in vitro* data has not been established *[see Drug Interactions (7.3)]*.

No *in vivo* drug interaction studies have been conducted with STELARA®.

Population pharmacokinetic data analyses indicated that the clearance of ustekinumab was not impacted by concomitant MTX, NSAIDs, and oral corticosteroids, or prior exposure to a TNF blocker in patients with psoriatic arthritis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of STELARA®. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, prior to and during early pregnancy.

13.2 Animal Toxicology and/or Pharmacology

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection.

14 CLINICAL STUDIES

14.1 Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled studies (Ps STUDY 1 and Ps STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies.

Ps STUDY 1 enrolled 766 subjects and Ps STUDY 2 enrolled 1230 subjects. The studies had the same design through Week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of STELARA®. Subjects randomized to STELARA® received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA® (either 45 mg or 90 mg) at Weeks 12 and 16.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

In both studies, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in Ps STUDY 1 and 40% of subjects in Ps STUDY 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of subjects had a history of psoriatic arthritis.

STELARA® (ustekinumab)

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 5 below.

Table 5: Clinical Outcomes Ps STUDY 1 and Ps STUDY 2

Week 12	Ps STUDY 1			Ps STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	255	255	256	410	409	411
PASI 75 response	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PGA of Cleared or Minimal	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)

Examination of age, gender, and race subgroups did not identify differences in response to STELARA® among these subgroups.

In subjects who weighed 100 kg or less, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 6 below).

Table 6: Clinical Outcomes by Weight Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			Ps STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response at Week 12*						
≤100 kg	4% 6/166	74% 124/168	65% 107/164	4% 12/290	73% 218/297	78% 225/289
>100 kg	2% 2/89	54% 47/87	68% 63/92	3% 3/120	49% 55/112	71% 86/121
PGA of Cleared or Minimal at Week 12*						
≤100 kg	4% 7/166	64% 108/168	63% 103/164	5% 14/290	74% 220/297	75% 216/289
>100 kg	3% 3/89	49% 43/87	58% 53/92	3% 4/120	51% 57/112	69% 84/121

* Patients were dosed with study medication at Weeks 0 and 4.

Subjects in Ps STUDY 1 who were PASI 75 responders at both Weeks 28 and 40 were re-randomized at Week 40 to either continued dosing of STELARA® (STELARA® at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to STELARA® treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks.

14.2 Psoriatic Arthritis

The safety and efficacy of STELARA® was assessed in 927 patients (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled studies in adult patients 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Patients were randomized to receive treatment with STELARA® 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)-α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the patients had been previously treated with TNF blocker, of whom over 70% had discontinued their TNF blocker treatment for lack of efficacy or intolerance at any time.

Clinical Response

In both studies, a greater proportion of patients achieved ACR 20, ACR 50 and PASI 75 response in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 7). ACR 70 responses were also higher in the STELARA® 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in STUDY 2. Responses were similar in patients regardless of prior TNFα exposure.

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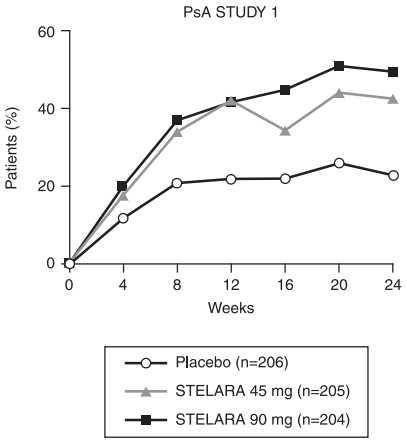
Table 7: ACR 20, ACR 50, ACR 70 and PASI 75 responses in PsA STUDY 1 and PsA STUDY 2 at Week 24

	PsA STUDY 1			PsA STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Number of patients randomized	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)	7 (7%)	18 (17%)	24 (23%)
ACR 70 response, N (%)	5 (2%)	25 (12%)	29 (14%)	3 (3%)	7 (7%)	9 (9%)
Number of patients with ≥ 3% BSA[a]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)

[a] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

The percent of patients achieving ACR 20 responses by visit is shown in Figure 1.

Figure 1: Percent of patients achieving ACR 20 response through Week 24



The results of the components of the ACR response criteria are shown in Table 8.

Table 8: Mean change from baseline in ACR components at Week 24

	PsA STUDY 1		
		STELARA®	
	Placebo (N=206)	45 mg (N= 205)	90 mg (N= 204)
Number of swollen joints[a]			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints[b]			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Patient's assessment of pain[c]			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Patient global assessment[c]			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment[c]			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ)[d]			
Baseline	1.2	1.2	1.2
Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)[e]			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

[a] Number of swollen joints counted (0-66)
[b] Number of tender joints counted (0-68)
[c] Visual analogue scale; 0= best, 10=worst.
[d] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.
[e] CRP: (Normal Range 0.0-1.0 mg/dL)

An improvement in enthesitis and dactylitis scores was observed in each STELARA® group compared with placebo at Week 24.

Physical Function

STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by HAQ-DI at Week 24. In both studies, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24.

14.3 Crohn's Disease

STELARA® was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy.

Studies CD-1 and CD-2

In studies CD-1 and CD-2, 1409 patients were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, patients were randomized to receive a single intravenous administration of STELARA® at either approximately 6 mg/kg, placebo (see Table 1), or 130 mg (a lower dose than recommended).

In Study CD-1, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 319 in the STELARA® approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator (6-mercaptopurine, azathioprine, methotrexate; 68% of patients), or both (49% of patients). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 286 in the STELARA® and 290 in the placebo group.

In these induction studies, a greater proportion of patients treated with STELARA® achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 9 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in STELARA® treated patients and continued to improve through Week 8.

Table 9: Induction of Clinical Response and Remission in CD-1* and CD-2**

	CD-1 n=741			CD-2 n=627		
	Placebo N=247	STELARA®† N=249	Treatment difference and 95% CI	Placebo N=209	STELARA®† N=209	Treatment difference and 95% CI
Clinical Response (100 point), Week 6	53 (21%)	84 (34%)[a]	12% (4%, 20%)	60 (29%)	116 (56%)[b]	27% (18%, 36%)
Clinical Remission, Week 8	18 (7%)	52 (21%)[b]	14% (8%, 20%)	41 (20%)	84 (40%)[b]	21% (12%, 29%)
Clinical Response (100 point), Week 8	50 (20%)	94 (38%)[b]	18% (10%, 25%)	67 (32%)	121 (58%)[b]	26% (17%, 35%)
70 Point Response, Week 6	75 (30%)	109 (44%)[a]	13% (5%, 22%)	81 (39%)	135 (65%)[b]	26% (17%, 35%)
70 Point Response, Week 3	67 (27%)	101 (41%)[a]	13% (5%, 22%)	66 (32%)	106 (51%)[b]	19% (10%, 28%)

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Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission: 70 point response is defined as reduction in CDAI score by at least 70 points

* Patient population consisted of patients who failed or were intolerant to TNF blocker therapy

** Patient population consisted of patients who failed or were intolerant to corticosteroids or immunomodulators (e.g., 6-mercaptopurine, azathioprine, methotrexate) and previously received but not failed a TNF blocker or were never treated with a TNF blocker.

† Infusion dose of STELARA® using the weight-based dosage regimen specified in Table 1.

[a] $0.001 \leq p < 0.01$

[b] $p < 0.001$

Study CD-3

The maintenance study (CD-3), evaluated 388 patients who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 of induction with STELARA® in studies CD-1 or CD-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks or placebo for 44 weeks (see Table 10).

Table 10: Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* N=131†	**90 mg STELARA® every 8 weeks N=128†**	**Treatment difference and 95% CI**
Clinical Remission	47 (36%)	68 (53%)[a]	17% (5%, 29%)
Clinical Response	58 (44%)	76 (59%)[b]	15% (3%, 27%)
Clinical Remission in patients in remission at the start of maintenance therapy**	36/79 (46%)	52/78 (67%)[a]	21% (6%, 36%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to STELARA® and were randomized to receive placebo at the start of maintenance therapy.

** Patients in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.

† Patients who achieved clinical response to STELARA® at the end of the induction study.

[a] $p < 0.01$

[b] $0.01 \leq p < 0.05$

At Week 44, 47% of patients who received STELARA® were corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group.

At Week 0 of Study CD-3, 34/56 (61%) STELARA® treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44.

At Week 0 of Study CD-3, 46/72 (64%) STELARA® treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of STELARA® treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

Patients who were not in clinical response 8 weeks after STELARA® induction were not included in the primary efficacy analyses for Study CD-3; however, these patients were eligible to receive a 90 mg subcutaneous injection of STELARA® upon entry into Study CD-3. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

15 REFERENCES

[1] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 6.6.2 Regs Research Data, Nov 2009 Sub (1973-2007) - Linked To County Attributes - Total U.S., 1969-2007 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2010, based on the November 2009 submission.

STELARA® (ustekinumab)

16 HOW SUPPLIED/STORAGE AND HANDLING

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to slightly yellow solution. STELARA® is available in single-dose prefilled syringes containing 45 mg or 90 mg or single-dose vials containing 45 mg of ustekinumab for subcutaneous use. Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber.

STELARA® is also available in single-dose vials containing 130 mg ustekinumab for intravenous use.

Subcutaneous Use	**NDC**
45 mg/0.5 mL single-dose prefilled syringe	57894-060-03
90 mg/mL single-dose prefilled syringe	57894-061-03
45 mg/0.5 mL single-dose vial	57894-060-02
Intravenous Infusion	**NDC**
130 mg/26 mL (5 mg/mL) single-dose vial	57894-054-27

Storage and Stability

STELARA® vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store STELARA® vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use)

Infections

Inform patients that STELARA® may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients of the risk of developing malignancies while receiving STELARA® *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

- Advise patients to seek immediate medical attention if they experience any signs or symptoms of serious hypersensitivity reactions and discontinue STELARA® *[see Warnings and Precautions (5.5)]*.
- Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex *[see Dosage and Administration (2.4)]*

Immunizations

Inform patients that STELARA® can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions (5.7)]*.

Pregnancy Registry

Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to STELARA® *[see Use in Specific Populations (8.1)]*.

Administration

Instruct patients to follow sharps disposal recommendations, as described in the Instructions for Use.

Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Cilag AG, Schaffhausen, Switzerland

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MEDICATION GUIDE
STELARA (stel ar' a)
(ustekinumab)
injection, for subcutaneous or intravenous use

What is the most important information I should know about STELARA?

STELARA is a medicine that affects your immune system. STELARA can increase your risk of having serious side effects, including:

Serious infections: STELARA may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections while taking STELARA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.

- Your doctor should check you for TB before starting STELARA.
- If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with STELARA and during treatment with STELARA.
- Your doctor should watch you closely for signs and symptoms of TB during treatment with STELARA.

You should not start taking STELARA if you have any kind of infection unless your doctor says it is okay.

Before starting STELARA, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have TB, or have been in close contact with someone with TB.

After starting STELARA, call your doctor right away if you have any symptoms of an infection (see above). STELARA can make you more likely to get infections or make an infection that you have worse. People who have a genetic problem where the body does not make any of the proteins interleukin 12 (IL-12) and interleukin 23 (IL-23) are at a higher risk for certain serious infections. These infections can spread throughout the body and cause death. People who take STELARA may also be more likely to get these infections.

Cancers

STELARA may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your doctor if you have ever had any type of cancer. Some people who are receiving STELARA and have risk factors for skin cancer have developed certain types of skin cancers. During your treatment with STELARA, tell your doctor if you develop any new skin growths.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS):

RPLS is a rare condition that affects the brain and can cause death. The cause of RPLS is not known. If RPLS is found early and treated, most people recover. Tell your doctor right away if you have any new or worsening medical problems including:

- headache
- seizures
- confusion
- vision problems

What is STELARA?

STELARA is a prescription medicine used to treat adults 18 years and older with:

- moderate or severe psoriasis that involves large areas or many areas of their body, who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).
- active psoriatic arthritis. STELARA can be used alone or with methotrexate.
- moderately to severely active Crohn's disease in people who have already taken other medicine that did not work well enough or they could not tolerate it.

STELARA may improve your psoriasis, psoriatic arthritis or Crohn's disease, but may also lower the ability of your immune system to fight infections. Taking STELARA may also increase your risk for certain types of cancer.

It is not known if STELARA is safe and effective in children.

Do not take STELARA if you are allergic to ustekinumab or any of the ingredients in STELARA. See the end of this Medication Guide for a complete list of ingredients in STELARA.

Before you receive STELARA, tell your doctor if you:

- have any of the conditions or symptoms listed in the section **"What is the most important information I should know about STELARA?"**
- ever had an allergic reaction to STELARA. Ask your doctor if you are not sure.
- are allergic to latex. The needle cover on the prefilled syringe contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who take STELARA should not receive live vaccines. Tell your doctor if anyone in your house needs a vaccine. The viruses used in some types of vaccines can spread to people with a weakened immune system, and can cause serious problems. **You should not receive the BCG vaccine during the one year before taking STELARA or one year after you stop taking STELARA.**
- have any new or changing lesions within psoriasis areas or on normal skin.
- are receiving or have received allergy shots, especially for serious allergic reactions. Allergy shots may not work as well for you during treatment with STELARA. STELARA may also increase your risk of having an allergic reaction to an allergy shot.
- receive or have received phototherapy for your psoriasis.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if STELARA can harm your unborn baby. You and your doctor should decide if you will take STELARA. There is a pregnancy registry for women who take STELARA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you are pregnant or become pregnant while taking STELARA, talk to your doctor about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.
- are breastfeeding or plan to breastfeed. It is thought that STELARA passes into your breast milk in small amounts.
- Talk to your doctor about the best way to feed your baby if you take STELARA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use STELARA?

- Use STELARA exactly as prescribed by your doctor.
- **The needle cover on the STELARA prefilled syringe contains latex. Do not handle the needle cover if you are sensitive to latex.**
- Adults with Crohn's disease will receive the first dose of STELARA through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. It takes at least 1 hour to receive the full dose of medicine. You will then receive STELARA as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of STELARA, as described below.
- Adults with psoriasis or psoriatic arthritis will receive STELARA as an injection under the skin (subcutaneous injection) as described below.
- **Injecting STELARA under your skin**
  - If your doctor decides that you or a caregiver may give your injections of STELARA at home, you should receive training on the right way to prepare and inject STELARA. Do not try to inject STELARA yourself until you or your caregiver have been shown how to inject STELARA by your doctor or nurse.
  - Inject STELARA under the skin (subcutaneous injection) in your upper arms, buttocks, upper legs (thighs) or stomach area (abdomen).
  - Do not give an injection in an area of the skin that is tender, bruised, red or hard.
  - Use a different injection site each time you use STELARA.
  - If you inject more STELARA than prescribed, call your doctor right away.
  - Be sure to keep all of your scheduled follow-up appointments.
- **Read the detailed Instructions for Use at the end of this Medication Guide for instructions about how to prepare and inject a dose of STELARA, and how to properly throw away (dispose of) used needles and syringes.**

What should I avoid while using STELARA?

You should not receive a live vaccine while taking STELARA. See **"What should I tell my doctor before receiving STELARA?"**

What are the possible side effects of STELARA?

STELARA may cause serious side effects, including:

- See **"What is the most important information I should know about STELARA?"**
- **Serious allergic reactions.** Serious allergic reactions can occur with STELARA. Stop using STELARA and get medical help right away if you have any of the following symptoms of a serious allergic reaction:
  - feeling faint
  - swelling of your face, eyelids, tongue, or throat
  - chest tightness
  - skin rash

Common side effects of STELARA include:

- upper respiratory infections
- headache
- tiredness
- itching
- vomiting
- vaginal yeast infections
- urinary tract infections
- redness at the injection site

These are not all of the possible side effects of STELARA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Janssen Biotech, Inc. at 1-800 JANSSEN (1-800-526-7736).

How should I store STELARA?

- Store STELARA prefilled syringes in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Store STELARA in the original carton to protect it from light until time to use it.
- Do not freeze STELARA.
- Do not shake STELARA.

Keep STELARA and all medicines out of the reach of children.

General information about the safe and effective use of STELARA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use STELARA for a condition for which it was not prescribed. Do not give STELARA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your doctor or pharmacist for information about STELARA that was written for health professionals.

What are the ingredients in STELARA?

Active ingredient: ustekinumab

Inactive ingredients: single-dose prefilled syringe contains L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, and sucrose. **Single-dose vial** contains L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80 and sucrose.

Manufactured by: Janssen Biotech , Inc., Horsham, PA 19044, US License No. 1864

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For more information, go to *www.stelarainfo.com* or call 1-800-JANSSEN (1-800-526-7736).

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: 09 2016

janssen

INSTRUCTIONS FOR USE
STELARA (stel ar' a**)**
(ustekinumab)
injection, for subcutaneous use

Instructions for injecting STELARA using a prefilled syringe.

Read this Instructions for Use before you start using STELARA. Your doctor or nurse should show you how to prepare and give your injection of STELARA the right way.

If you cannot give yourself the injection:

- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

Do not try to inject STELARA yourself until you have been shown how to inject STELARA by your doctor, nurse or health professional.

Important information:

- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
  - If your dose is 45 mg, you will receive one 45 mg prefilled syringe.
  - If your dose is 90 mg, you will receive either one 90 mg prefilled syringe or two 45 mg prefilled syringes. **If you receive two 45 mg prefilled syringes for a 90 mg dose, you will need to give yourself two injections, one right after the other.**
- Check the expiration date on the pre-filled syringe and carton. If the expiration date has passed, do not use it. If the expiration date has passed call your doctor or pharmacist, or call 1-800-JANSSEN (1-800-526-7736) for help.
- Make sure the syringe is not damaged.
- **The needle cover on the prefilled syringe contains latex. Do not handle the needle cover on the STELARA prefilled syringe if you are sensitive to latex.**
- Check your prefilled syringe for any particles or discoloration. Your prefilled syringe should look clear and colorless to light yellow with few white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new prefilled syringe.
- **Do not shake the prefilled syringe at any time.** Shaking your prefilled syringe may damage your STELARA medicine. If your prefilled syringe has been shaken, do not use it. Get a new prefilled syringe.
- To reduce the risk of accidental needle sticks, each prefilled syringe has a needle guard that is automatically activated to cover the needle after you have given your injection. Do not pull back on the plunger at any time.

Gather the supplies you will need to prepare and to give your injection. (See Figure A)

You will need:

- antiseptic wipes
- cotton balls or gauze pads
- adhesive bandage
- your prescribed dose of STELARA **(See Figure B)**
- FDA-cleared sharps disposal container. **See "Step 4: Dispose of the syringe."**

Figure A

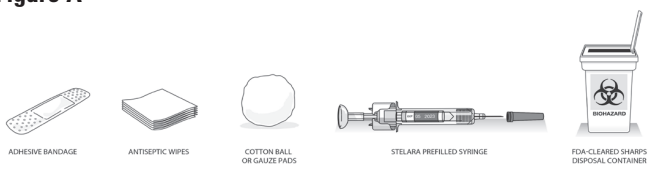
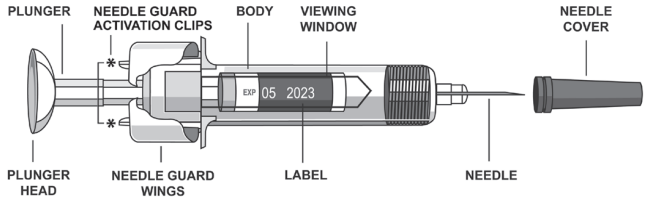


Figure B



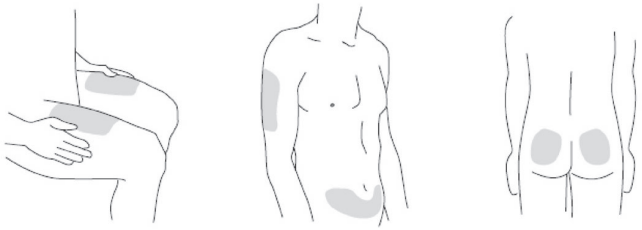
Step 1: Prepare the injection.

- Choose a well lit, clean, flat work surface.
- Wash your hands well with soap and warm water.
- Hold the prefilled syringe with the covered needle pointing upward.

Step 2: Prepare your injection site

- Choose an injection site around your stomach area (abdomen), buttocks, upper legs (thighs). If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(See Figure C)**
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give your injection.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

Figure C

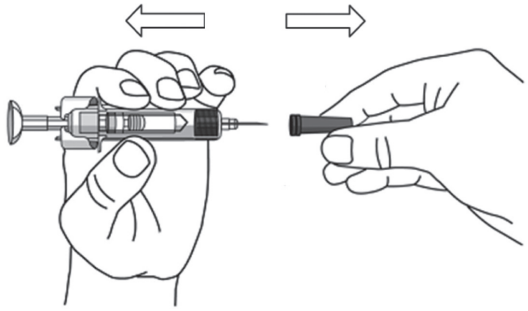


*Areas in gray are recommended injection sites.

Step 3: Inject STELARA

- Remove the needle cover when you are ready to inject your STELARA.
- **Do not** touch the plunger while removing the needle cover.
- Hold the body of the prefilled syringe with one hand, and pull the needle cover straight off. **(see Figure D)**
- Put the needle cover in the trash.
- You may also see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch the needle or let it touch anything.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place. Call your doctor, nurse or health professional for instructions.

Figure D



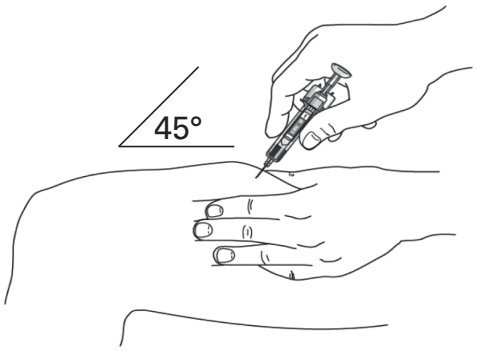
- Hold the body of the prefilled syringe in one hand between the thumb and index fingers. **(See Figure E)**

Figure E



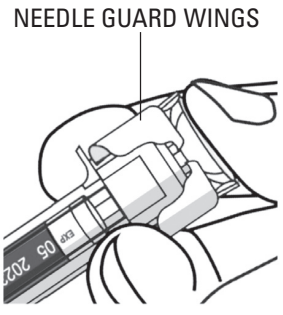
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure F)**

Figure F



- Inject all of the liquid by using your thumb to push in the plunger until the plunger head is completely between the needle guard wings. **(See Figure G)**

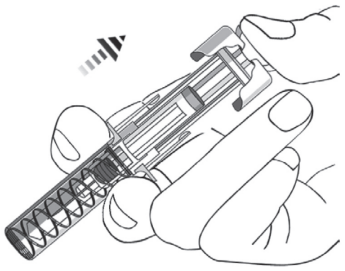
Figure G



STELARA® (ustekinumab)

- When the plunger is pushed as far as it will go, keep pressure on the plunger head. Take the needle out of the skin and let go of the skin.
- Slowly take your thumb off the plunger head. This will let the empty syringe move up until the entire needle is covered by the needle guard. **(See Figure H)**

Figure H



- When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

Step 4: Dispose of the syringe.

- Put the syringe in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic.
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out.
  - upright and stable during use,
  - leak-resistant,
  - and properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your sharps disposal container.
- If you have any questions, talk to your doctor or pharmacist.

Keep STELARA and all medicines out of the reach of children.

Prefilled Syringe Manufactured by:
Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864
at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and
at Cilag AG, Schaffhausen, Switzerland

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Issued 09/2016

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https://web.archive.org/web/20170712033550/https://www.pmda.go.jp/files/000153747.pdf

Report on the Deliberation Results

December 6, 2010

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name]	Ustekinumab (Genetical Recombination) (JAN*)
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	January 21, 2010

[Results of deliberation]
In the meeting held on November 29, 2010, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs.

The conditions for approval should be modified as follows.

After modification
[Conditions for approval]
The applicant is required to:
1. Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.
2. Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the efficacy and long-term safety of the product, including the occurrence of infections, etc.

Before modification
[Conditions for approval]
The applicant is required to:
1. Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.
2. Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the efficacy and long-term safety of the product and the occurrence of infections etc.

(The underlined parts are the changes.)

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version

Japanese Accepted Name (modified INN)

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version

Review Report

November 10, 2010
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010
[Dosage form/Strength] A solution for injection in a prefilled syringe. Each prefilled syringe (0.5 mL) contains 45 mg of Ustekinumab (Genetical Recombination).
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure] See Figure 1 and Figure 2 below.
Molecular formula: H-chain $C_{2207}H_{3410}N_{582}O_{671}S_{17}$
L-chain $C_{1034}H_{1596}N_{274}O_{337}S_{6}$
Molecular weight: 148,079 to 149,690
Chemical name:

Ustekinumab is a recombinant human IgG1 monoclonal antibody against the p40 subunit of human interleukin-12 and interleukin-23.
Ustekinumab is produced in mouse myeloma (Sp2/0) cells.
Ustekinumab is a glycoprotein (molecular weight, 148,079-149,690) composed of 2 H-chain (γ1-chain) molecules consisting of 449 amino acid residues each and 2 L-chain (κ-chain) molecules consisting of 214 amino acid residues each.

[Items warranting special mention] None
[Reviewing office] Office of New Drug IV

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version

Heavy Chain

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EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY   60
                          22-96
SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR PGQGYFDFWG QGTLVTVSSS  120

STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG  180
                     146-202
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP  240
                                   222 LC  228 HC  231 HC  N-Glycan
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS  300
                          263-323
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL  360

TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ  420
  369-427
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK                                    449
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Light Chain

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DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS   60
                          23-88
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ GTKLEIKRTV AAPSVFIFPP  120

SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
                134-194
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214
                                    HC
```

Figure 1. Heavy and light chains of ustekinumab

Amino acid sequences of the heavy and light chains of ustekinumab are indicated in the single-letter code.
Complementarity-determining regions are underlined.
H-chain K449: partial processing

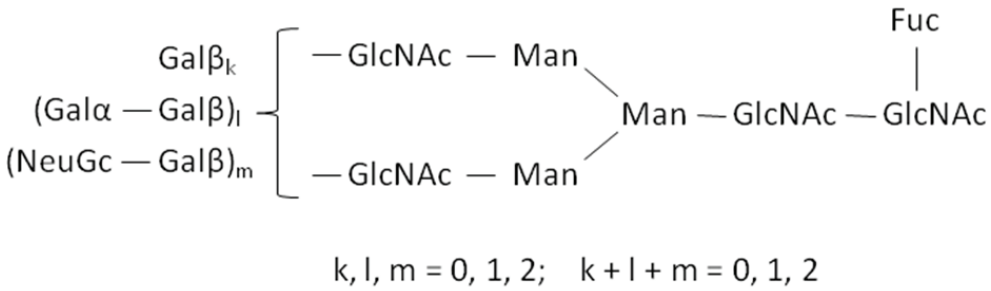


Figure 2. Carbohydrate structure

Review Results

November 10, 2010

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010

[Results of review]
Based on the submitted data, the efficacy of the product in the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy has been demonstrated and its safety is acceptable in view of its observed benefits.

Serious adverse drug reactions such as infections may occur following administration of the product. Therefore, prior to the use of the product, the patient's symptoms etc. should be monitored closely and the risks and benefits of the product should be weighed carefully. The risks of the product should be fully explained to the patient as well. It is necessary to closely monitor the course of the disease also after the initiation of treatment. After the market launch, a post-marketing surveillance study focusing on the occurrence of serious infections etc., covering all the patients treated with the product, and a long-term survey to follow the patients for the development of infections and malignancy etc. need to be conducted.

As a result of its review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

[Indication]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris and psoriatic arthritis

[Dosage and administration]
The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter. If the effect is insufficient, a dose of 90 mg may be used.

[Conditions for approval]
The applicant is required to:
(1) Conduct a post-marketing drug use-results survey, which covers all the patients treated with the

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product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.

(2) Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the long-term safety of the product and the occurrence of infections etc.

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Review Report (1)

October 12, 2010

I. Product Submitted for Registration

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010
[Dosage form/Strength] A solution for injection in a prefilled syringe. Each prefilled syringe (0.5 mL) contains 45 mg of Ustekinumab (Genetical Recombination).
[Proposed indication]
Moderate to severe psoriasis vulgaris
Psoriatic arthritis with moderate to severe plaque psoriasis
[Proposed dosage and administration]
The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter.
A dose of 90 mg may be administered in patients weighing >100 kg.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

The active substance Ustekinumab (Genetical Recombination) (ustekinumab) is a human immunoglobulin G (IgG) 1κ monoclonal antibody (mAb) against human interleukin (IL)-12/23 p40, developed by Centocor Inc. (the US) (currently Centocor Ortho Biotech Inc.).

Psoriasis vulgaris is an immune-mediated inflammatory keratosis with alternating periods of remissions and flare-ups, characterized by the formation of infiltrative erythematous plaques or irregularly shaped erythematous plaques. Psoriatic arthritis is a rheumatoid factor-negative inflammatory arthritis associated with psoriasis of skin. In general, for patients with mild (body surface area [BSA] involvement of ≤10%) to moderate (BSA involvement of 10%-30%) disease, topical corticosteroids, topical vitamin D_3 derivatives, and combination therapy of these agents are used. For patients with moderate to severe disease, phototherapy and systemic therapies (e.g., cyclosporine, and etretinate) are used. Anti-TNF-α agents, infliximab and adalimumab, were approved in January 2010 to treat patients who have had an inadequate response to these conventional therapies.

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T cells are believed to be fundamental to the development of the disease and to play a central role in the pathology of the disease. Ustekinumab has a novel mechanism of action of inhibiting the function of T cells by binding with high affinity to IL-12/23 p40, the shared subunit of human IL-12 and IL-23 that are involved in T cell differentiation. Thus, ustekinumab was developed as a therapeutic drug for psoriasis.

The clinical development of ustekinumab for the treatment of psoriasis began in 20[redacted] overseas and ustekinumab was first approved in Canada in December 2008 for the indication of "moderate to severe plaque psoriasis." As of September 2010, ustekinumab has been approved in 52 countries for indications related to psoriasis.

In Japan, the clinical development of ustekinumab for the treatment of psoriasis began in [redacted] 20[redacted]. Based on the claim that Japanese clinical studies etc. have confirmed the efficacy and safety of ustekinumab, the applicant has filed a marketing application for ustekinumab.

2. Data relating to quality

2.A Summary of the submitted data

Ustekinumab is produced in murine myeloma (Sp2/0) cells, and it is a glycoprotein (molecular weight, 148,079-149,690) composed of two heavy chain (γ1chain, $C_{2207}H_{3410}N_{582}O_{671}S_{17}$; molecular weight, 49,377.29) molecules consisting of 449 amino acid residues each and two light chain (κ-chain, $C_{1034}H_{1596}N_{274}O_{337}S_6$; molecular weight, 23,449.76) molecules consisting of 214 amino acid residues each. Ustekinumab contains a single *N*-linked glycosylation site (Asn299) in the constant region of each heavy chain. The molecule contains a total of 16 disulfide bonds.

2.A.(1) Drug substance manufacturing process

2.A.(1).1) Assembly of the gene expression construct and cell banking

[redacted]

A genomic library of the cell line A was prepared to clone human anti-IL-12 IgG1 heavy and light chain genes. [redacted]. A master cell bank (MCB) was prepared from the cell line D and a working cell bank (WCB) was

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prepared from the MCB. Although bovine serum was used in the process before the selection of the cell line D, no raw materials of animal origin were used thereafter.

2.A.(1).2) Characterization and control of cell banks

MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) were characterized as shown in Table 1.

Table 1. Results of characterization of cell banks etc.

Test	Test results			
	MCB	WCB		CAL
	Lot: a	Lot: b	Lot: c	Lot: d
Isoenzyme analysis	Of mouse origin	Of mouse origin	Of mouse origin	Of mouse origin
Double immunodiffusion	NT	[redacted]		NT
cDNA sequence	cDNA sequence/deduced amino acid sequence agreed with the reference sequence.	NT	NT	Consistent with MCB
Analysis of patterns of DNA inserts	Consistent with the banding patterns of the heavy and light chain vectors	NT	NT	Consistent with MCB
Gene copy number	[redacted]	NT	NT	[redacted]
[redacted]	NT	NT	NT	[redacted]

NT: Not tested

Purity tests as shown in Table 2 were performed and no viral or non-viral infectious agents were detected other than ecotropic recombinant virus (ERV) and A-type and C-type retrovirus-like particles in the MCB, WCB, and CAL, within the scope of the tests performed.

Table 2. Results of tests for purity of cell banks etc.

Test			Acceptance criteria	Test results			
				MCB	WCB		CAL
				Lot: a	Lot: b	Lot: c	Lot: d
Sterility			Negative	Negative	Negative	Negative	NT
Mycoplasma testing (culture method and non-cultural method)			Negative	Negative	Negative	Negative	NT
Tests for retroviruses and other endogenous viruses	Infectivity assays	Assay for ERV[a)]	Report results only	Negative	Negative	Negative	NT
		S^+L^- focus assay[b)]	Report results only	Negative	Negative	Negative	NT
		XC plaque assay[c)]	Report results only	Negative	Negative	Negative	NT
		Co-cultivation assay for ERV[a)]	Report results only	ERV detected	ERV detected	ERV detected	ERV detected
		Mink cell focus assay[c)]	Report results only	Negative	Negative	Negative	Negative
	Electron microscopy		Report results only	A-type and C-type retrovirus-like particles observed	A-type and C-type retrovirus-like particles observed	A-type and C-type retrovirus-like particles observed	A-type and C-type retrovirus-like particles observed
	Reverse transcriptase		Report results only	Reverse transcriptase detected	Reverse transcriptase detected	Reverse transcriptase detected	Reverse transcriptase detected
Tests for non-endogenous or adventitious viruses	*In vitro* assays	Assay for adventitious viruses[d)]	Negative	Negative	Negative	Negative	Negative
		Bovine virus assay[e)]	Negative	Negative	Negative	Negative	Negative
		Assay for adventitious bovine viruses derived from components other than bovine serum[f)]	Negative	Negative	NT	NT	Negative
	In vivo assays	Assay to reveal latent viruses[g)]	Negative	Negative	Negative	Negative	Negative
		Assay for mouse thymic virus	Negative	Negative	Negative	Negative	Negative
	Mouse antibody production test[h)]		Negative	Negative	Negative	Negative	Negative

NT: Not tested

a) *Mus dunni* cells were used.

b) $MiCl_1$ S^+L^- cells and Mv1Lu mink cells were used.

c) SC-1 cells were used.

d) MRC-5 cells, Vero cells, HeLa cells, Sp2/0 cells (MCB and WCB), and [redacted] indicator cell line (MCB and CAL) were used.

e) Bovine turbinate cells were used and immunostained for bovine adenovirus type 5, bovine parvovirus, bovine viral diarrhea virus, infectious bovine rhinotracheitis virus, and bovine parainfluenza virus type 3.

f) Bovine turbinate cells and Vero cells were used.

g) Inoculated into adult mice, suckling mice, and guinea pigs, and embryonated eggs.

h) polyoma virus, Sendai virus, lymphocytic choriomeningitis virus, ectromelia virus, reovirus type 3, K virus, minute virus of mice, pneumonia virus of mice, mouse hepatitis virus, mouse encephalomyelitis virus, mouse cytomegalovirus, mouse rotavirus, lactic dehydrogenase virus, Hantaan virus, mouse thymic virus, and mouse adenovirus were used. For Lot c of WCB and CAL, mouse parvovirus was also used.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. The MCB is stored at more than one site.

[redacted]

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[redacted]. A new WCB will be generated periodically.

2.A.(1).3) Manufacturing process

The manufacturing process for the drug substance is as shown below.

	Manufacturing process	In-process controls
Stage 1	**Preculture and Expansion** Thawing of WCB [redacted] Equipment: culture flasks, culture bags, and [redacted]-L bioreactor	
Stage 2	**Production Culture** [redacted] Equipment: [redacted]-L production bioreactor	bioburden, mycoplasma, and *in vitro* assay for adventitious viruses
Stage 3	[redacted]	[redacted]
Stage 4	**Thawing and pooling of [redacted] eluate**	
Stage 5	**Solvent/Detergent (S/D) Treatment** [redacted]	[redacted]
Stage 6	**Cation Exchange Chromatography** Carrier: [redacted]	bioburden and endotoxin
Stage 7	**Anion Exchange Chromatography** Carrier: [redacted]	bioburden and endotoxin
Stage 8	**Virus Removal Filtration** Filter: [redacted]	protein concentration, bioburden, and endotoxin
Stage 9	[redacted]	[redacted]
Stage 10	**Preparation of ustekinumab formulated bulk (FB)** [redacted] **Ustekinumab FB**	[redacted]

Note: Critical steps are enclosed in boxes.

[redacted]. The cause of the contamination with *Staphylococcus epidermidis* was identified and then measures were taken to prevent the recurrence.

Table 3. Attributes evaluated in process validation for each stage

Stages	Attributes evaluated
Stage 1	[redacted]
Stage 2	bioburden, *in vitro* assay for adventitious viruses, and mycoplasma testing (culture method and non-cultural method)
Stage 3	[redacted]
Stage 4	bioburden and endotoxin
Stage 5	[redacted]
Stage 6	[redacted]
Stage 7	[redacted]
Stage 8	[redacted]
Stage 9	[redacted]
Stage 10	[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

Furthermore, based on the stability evaluation of intermediates produced during the manufacturing process, the storage conditions and storage periods were determined.

2.A.(1).4) Adventitious agents safety evaluation

In the manufacturing process for the drug substance, no raw materials of animal origin were used other than Sp2/0 host cells.

Purity tests were performed on the MCB, WCB, and CAL and no viral or non-viral infectious agents were detected other than ERV, and A-type and C-type retrovirus-like particles [see "2.A.(1).2) Characterization and control of cell banks"]. [redacted] batches of culture fluid were evaluated for the presence of retrovirus (assay for ERV[1], S^+L^- focus assay[1], XC plaque assay[1], mink cell focus assay[1], electron microscopy[2]) in process validation and no retrovirus or adventitious virus was detected other

[1] Samples taken from bioreactor on around Day [redacted] or [redacted] of cell culture for productionwere evaluated.

[2] Samples taken from bioreactor on around Days [redacted], [redacted], and [redacted] of cell culture for productionwere evaluated. Note that samples on Day [redacted] instead of samples taken from bioreactor on around Day [redacted] were used for [redacted] of [redacted] batches were evaluated.

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than ERV and retrovirus-like particles. In-process testing is performed to ensure that the culture fluid at the end of the production run is free of mycoplasma and adventitious virus contamination.

In order to evaluate the capacity of the purification process to clear viruses, viral clearance studies were performed with relevant viruses and non-specific model viruses as shown in Table 4, which demonstrated that all viruses are adequately removed by the purification process. It has been discussed that the overall reduction factor for ERV indicates that the purification process provides adequate endogenous retrovirus clearance.

Table 4. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10}) (One-sided 95% confidence interval [CI] in parenthesis)			
	ERV	Poliovirus type 1	Reovirus type 3	Pseudorabies virus
Stage 3: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 5: S/D treatment	[redacted]	NT	NT	[redacted]
Stage 7: Anion exchange chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Stage 8: Viral removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>19.4 (1.0)	≥6.6 (0.7)	≥10.5 (0.9)	≥14.6 (0.8)

NT: Not tested

2.A.(1).5) Manufacturing process development (Comparability)

During the development of ustekinumab, changes were made to the manufacturing process in order to establish a robust manufacturing process for supplying a sufficient quantity of the drug product at an appropriate manufacturing-scale. The major changes are shown in Table 5.

Table 5. Major changes made to the manufacturing process

Manufacturing method	Manufacturing method A	Manufacturing method B	Manufacturing method C	Manufacturing method D
Intended use	Non-clinical studies, Foreign phase I clinical studies	Foreign phase II clinical studies: Psoriasis	Foreign phase II clinical studies: Psoriatic arthritis Multiple sclerosis	Foreign phase III clinical studies Japanese Study JPN-01 Japanese Study JPN-02 To-be-marketed drug product
Cell line[a]	B	Same as left	D	Same as left
[redacted]	Medium containing bovine-derived raw materials	Same as left	[redacted]	Same as left
[redacted]	[redacted]L	[redacted]L	[redacted]L	[redacted]L
[redacted]	[redacted]	[redacted]	Same as left	Same as left
[redacted]	[redacted]	[redacted]	[redacted]	Same as left
Virus removal membrane	[redacted] virus retentive filter	[redacted] virus retentive filter	Same as left	Same as left
[redacted]	Of animal origin	Same as left	Of plant origin	Same as left
Dosage form	Lyophilized	Same as left	Same as left	Liquid

a: The cell line B and the cell line D are derived from the same murine myeloma cell line.

[redacted]. The following tests for the comparability exercise were conducted, which demonstrated comparability between the drug substances produced by Manufacturing Methods A and B.

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SDS-PAGE, size exclusion chromatography (SE-HPLC), charge heterogeneity (isoelectric focusing [IEF], ion exchange chromatography [IE-HPLC]), potency (a cell-based assay), and process-related impurities (bioburden, endotoxin, residual Protein A, bovine IgG)

For Manufacturing Method C, the cell line and medium etc. were changed. The following tests for the comparability exercise of the drug substances/drug products produced by Manufacturing Methods A and C were conducted.

Peptide mapping, N-terminal amino acid sequencing, circular dichroism spectra (far-ultraviolet, near-ultraviolet), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS), electrospray ionization mass spectrometry (ESI-MS), oligosaccharide mapping, SDS-PAGE, SE-HPLC, charge heterogeneity (IEF, IE-HPLC), potency (a cell-based assay), process-related impurities (HCP, host cell DNA, residual Protein A), degradation profile and degradation rate

[redacted]. Other test results were similar. In addition, a non-clinical study in cynomolgus monkeys showed no differences in pharmacokinetic parameters between products manufactured by method A and C [see "3.(ii) Summary of pharmacokinetic studies"]. These results demonstrated comparability between pre-change and post-change drug substances/drug products.

[redacted].The following tests for the comparability exercise were conducted, which demonstrated comparability between the drug products produced by Manufacturing Methods C and D.

Peptide mapping, N-terminal amino acid sequencing, circular dichroism spectra (far-ultraviolet, near-ultraviolet), differential scanning calorimetry, sedimentation coefficient, ESI-MS, oligosaccharide mapping, SDS-PAGE, SE-HPLC, charge heterogeneity (IEF, IE-HPLC), potency (a cell-based assay), degradation profile and degradation rate, product-related impurities (aggregates, truncated forms), and process-related impurities (HCP, host cell DNA, residual Protein A)

2.A.(2) Drug substance

2.A.(2).1) Structure and composition

The drug substance has been characterized as follows.

2.A.(2).1).(a) Primary structure

● The amino acid sequence of ustekinumab, as determined by N-terminal amino acid sequencing by Edman degradation and peptide mapping, agreed with the one deduced from cDNA.

● Heterogeneity in C-terminal Lys residues of the heavy chain, which is commonly observed in IgG1,

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was detected by LC/electrospray ionization quadrupole time-of-flight mass spectrometry (ESI-QTOF MS).

2.A.(2).1).(b) Higher order structure

● Two intra-chain disulfide bonds in each light chain, four intra-chain disulfide bonds in each heavy chain, and four inter-chain disulfide bonds (two inter-heavy chain disulfide bonds in the hinge region, one inter-heavy-light chain disulfide bond for each heavy and light chain pair) were identified by peptide mapping under non-reducing conditions. Free sulfhydryl analysis using Ellman's reagent revealed that [redacted]% of all Cys residues are present as free sulfhydryl groups, confirming that almost all Cys residues are involved in disulfide bond formation, as is the case with a typical IgG1.

● [redacted].

● [redacted]

● The sedimentation coefficient as determined by sedimentation velocity analytical ultracentrifugation (SV-AUC) was typical of IgG.

● The apparent molecular weight of ustekinumab, as measured by sedimentation equilibrium AUC, was approximately [redacted], which was close to the molecular weights of different glycoforms of ustekinumab, approximately 148,000 to 150,000, as measured by mass spectrometry, indicating that the molecule is monomeric in solution.

● Differential scanning calorimetry analysis showed that ustekinumab has a folded structure, with a thermally stable conformation.

2.A.(2).1).(c) Carbohydrate structure

● Fragment analysis by peptide mapping showed that ustekinumab is glycosylated at Asn299 of the heavy chain.

● Analysis of neutral monosaccharide composition indicated that ustekinumab has a biantennary, core-fucosylated *N*-glycan with galactose heterogeneity. No galactosamine was detected, indicating the absence of *O*-linked glycosylation.

● Oligosaccharide mapping and sequential exoglycosidase digestion revealed that ustekinumab has [redacted] types of biantennary, core-fucosylated glycans with galactose and sialic acid heterogeneity. Neutral oligosaccharides (G0F, [redacted]%; G1F, [redacted]%; G2F, [redacted]%) and sialylated oligosaccharides accounted for [redacted]% and [redacted]%, respectively, of the total glycans.

● The results of sialic acid analysis revealed that [redacted]% of the total sialic acid was *N*-glycolylneuraminic acid (NGNA) and [redacted]% was *N*-acetylneuraminic acid (NANA).

2.A.(2).1).(d) Isoforms

● The mass spectrum showed multiple peaks due to the heterogeneity among multiple *N*-glycan structures and partial removal of heavy chain C-terminal Lys. After removing the heavy chain C-terminal Lys residues, the mass spectrum revealed only peaks derived from different *N*-glycans.

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● After removing the heavy chain C-terminal Lys residues, both IEF and cIEF profiles revealed [redacted] isoforms in the pI range of [redacted] to [redacted]. Further analyses by IE-HPLC and peptide mapping revealed isoforms with oligosaccharides containing [redacted] to [redacted] sialic acids and those with neutral oligosaccharides.

● The mass spectra of blood samples from the patients treated with ustekinumab produced by the cell line B revealed [redacted] major isoforms. The clearance profiles of these isoforms in the serum over time were similar.

2.A.(2).1).(e) Other physicochemical properties

● The extinction coefficient was [redacted] $(mg/mL)^{-1}cm^{-1}$.

2.A.(2).1).(f) Biological properties

● Enzyme immunoassay (EIA) and surface plasmon resonance etc. showed that ustekinumab binds specifically to human IL-12 and human IL-23.

● The equilibrium constants for ustekinumab binding to human IL-12 and human IL-23 were [redacted] pmol/L and [redacted] pmol/L, respectively.

● Ustekinumab inhibited human IL-12 and human IL-23 from binding to their receptors (human IL-12Rβ1, human IL-12Rβ1/β2 receptor complex, human IL-12Rβ1/23R receptor complex) by binding to human IL-12/23p40. Ustekinumab could not bind to human IL-12 or human IL-23 that was already bound to their receptors, resulting in no induction of complement dependent cytotoxicity (CDC) [see "3.(i) Summary of pharmacology studies"].

● In an *in vitro* assay using human H cells, ustekinumab was shown to inhibit human IL-12-induced IFN-γ production. In [redacted]-month stability studies at 5°C, [redacted]°C, and [redacted]°C, the activity of ustekinumab decreased over time when stored at [redacted]°C and [redacted]°C, showing that this assay presents the biological properties of ustekinumab for stability evaluation.

● [redacted].

● As to the binding of the Fc region of ustekinumab to [redacted] receptor and [redacted] receptor, the 50% effective concentration (EC50) in [redacted] binding assay was approximately [redacted] ng/mL and the 50% inhibitory concentration (IC50) in [redacted] competitive binding assay was [redacted] to [redacted] μg/mL.

2.A.(2).2) Product-related substances

[redacted].

● [redacted].

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● Since heavy chain C-terminal Lys residues are removed immediately by enzyme in serum or plasma, the presence or absence of C-terminal Lys residues of the heavy chain is not considered to have an impact on the potency, efficacy, or safety of ustekinumab. Thus, the variants produced due to the loss of C-terminal Lys residue of the heavy chain were considered to be product-related substances.

● [redacted].

2.A.(2).3) Impurities

2.A.(2).3).(a) Process-related impurities

[redacted]. All the process-related impurities have been demonstrated to be consistently and adequately removed in the manufacturing process [see "2.A.(1).3) Manufacturing process"].

2.A.(2).3).(b) Product-related impurities

[redacted]. Based on the results of assessment of the capacity of the manufacturing process to remove impurities, aggregates have been demonstrated to be removed consistently in the manufacturing process [see "2.A.(1).3) Manufacturing process"].

2.A.(2).4) Drug substance specifications

[redacted].

2.A.(2).5) Stability of drug substance

Using manufacturing-scale batches of drug substance, long-term testing ([redacted]°C [redacted] months, 4 batches; [redacted] months, 3 batches; [redacted] months, 2 batches] and [redacted]°C [redacted] months, 4 batches]), intermediate testing ([redacted]°C [redacted] months, 3 batches; [redacted] months, 2 batches; [redacted] months, 4 batches]), and accelerated testing ([redacted]°C [redacted] months, 9 batches]) were conducted. In all the studies, polycarbonate bottles with polypropylene caps were used to store drug substance samples.

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[redacted]

At the long-term storage condition, no changes over time occurred throughout the testing period at either [redacted]°C or [redacted]°C, except for a transient increase in potency at [redacted] months for [redacted] batches stored at [redacted]°C. In the intermediate storage condition ([redacted]°C), [redacted] batches showed a decrease in potency at [redacted] months of storage, but no other changes over time were observed at ≥[redacted] months of storage. No changes over time occurred for other attributes tested.

Based on the above stability data, a shelf life of [redacted] months was proposed for the drug substance when stored at ≤[redacted]°C.

2.A.(3) Drug product

2.A.(3).1) Formulation development

[redacted]. The proposed product is supplied in a prefilled glass syringe with a stainless needle and each prefilled syringe contains a volume of the drug solution that is sufficient to ensure delivery of 45 mg of ustekinumab. Each prefilled syringe is equipped with a needle safety guard (UltraSafe Passive Delivery System) (needle guard). A carton is used as the secondary packaging.

2.A.(3).2) Drug product manufacturing process

The manufacturing process for the drug product is as shown below.

	Manufacturing process	In-process controls
Step 1	**Thawing of FB**	
Step 2	**Pooling and Mixing**[1)]	Bioburden and Endotoxin
Step 3	[redacted]	Bioburden and Endotoxin
Step 4	**Sterile filtration**	Filter integrity
Step 5	**Filling**[2)]	[redacted]
Step 6	**Assembly**	
Step 7	**Secondary packaging**	
Step 8	**Testing, Storage**	

[1)]: FB is pooled into the mixer (Step 2) within [redacted] hours after start of thawing (Step 1).
[2)]: Filling is started within [redacted] hours after start of pooling of thawed FB (Step 1) into the mixer (Step 2).
Filling is completed within [redacted] hours.

[redacted]. As a result, the pre-determined acceptance criteria were met for all theattributes evaluated or the quality of the drug product was not affected, showing that the drug product of consistent quality can be manufactured. For

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[redacted] batches of another drug product to be supplied in a similar prefilled syringe (with a needle guard), no malfunction of the needle guard fitted in the assembly step was observed. Step [redacted] was defined as a critical step.

2.A.(3).3) Manufacturing process development

A liquid formulation for intravenous administration or a lyophilized formulation for subcutaneous administration was used in foreign phase I and phase II clinical studies. Another liquid formulation for subcutaneous administration was used in foreign phase III and Japanese phase I clinical studies. Furthermore, the liquid formulation for subcutaneous administration in a prefilled syringe (the liquid formulation in a prefilled syringe) was used in a Japanese phase II/III study. The liquid formulation in a prefilled syringe equipped with a needle guard is proposed for marketing.

2.A.(3).4) Drug product specifications

[redacted]

2.A.(3).5) Stability of drug product

Using manufacturing-scale batches of the drug product, long-term testing, accelerated testing, stress testing, photostability testing, and cycle tests were performed. The attributes tested are shown in Table 6.

Table 6. Stability studies on drug product

	Test conditions	Attributes tested
Long-term testing	2°C−8°C (24 months, 5 batches)	[redacted]
Accelerated testing	25°C ([redacted] months, 5 batches)	[redacted]
Stress testing	[redacted]°C ([redacted] months, 5 batches)	[redacted]
Photostability testing	[redacted]°C, an overall illumination of 1.2 million lux·hr and an integrated near ultraviolet energy of 200 W·h/m^2, 1 batch[1)]	[redacted]
Cycle tests	Condition 1[2)] and Condition 2[3)], 2 batches each	[redacted]

[1)] Three types of packaging were used in the study: (a) Primary packaging only (a glass syringe), (b) Primary and Secondary packaging (a carton), (c) Primary and Secondary packaging plus aluminum foil.

[2)] [redacted]

[3)] [redacted]

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[redacted].

[redacted].

[redacted]. No significant changes occurred for other attributes tested throughout the testing period.

[redacted]. In the samples of the drug product with primary and secondary packages compared to the samples of the drug product further wrapped with aluminum foil, changes from the initial time point in the IEF pattern were observed, but when a higher-sensitivity method, cIEF, was used, no changes in the cIEF pattern were noted, nor were any changes observed for other attributes tested.

Cycle tests were performed to evaluate the effect of short-term excursions outside the predetermined temperature range during shipping, storage, and use of the product. In the cycle test 1, a slight decrease in potency was observed after [redacted] cycles, but no significant changes were observed for other attributes tested throughout the testing period. In the cycle test 2, no significant changes were observed for the tested attributes throughout the testing period.

Based on the above stability data, a shelf life of 18 months was proposed for the drug product when stored at 2°C to 8°C and protected from light.

2.A.(4) Reference materials

[redacted]

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[redacted]

[redacted].

2.B Outline of the review

PMDA reviewed the submitted data, including the following major considerations, and concluded that the quality of the product is adequately controlled.

2.B.(1) Safety of non-human glycan structures

Non-human glycan structures are present in ustekinumab: sialylated oligosaccharides containing a non-human sialic acid NGNA ([redacted]% of the total glycans) and oligosaccharides containing a non-human Galα1-3Gal. PMDA asked the applicant to explain whether there is a safety concern about administering ustekinumab containing these non-human glycan structures.

The applicant explained as follows:

The glycans of ustekinumab are constrained in the internal cavity enclosed by the two polypeptide backbones of the CH2 domains of the Fc region and sterically shielded so that other molecules have limited access to these glycans. Therefore, these glycans are not considered to be antigenic or immunogenic (Dalziel M, McFarlane I, Axford JS., *Glycoconj J*. 1999;16: 801-7). Based on the clinical experience with ustekinumab in >2000 patients in Japan and overseas, no allergy-related serious adverse events after the initial or repeated doses have been reported and the incidence of anti-ustekinumab antibody development was low, suggesting that oligosaccharides containing NGNA or Galα1-3Gal in ustekinumab are unlikely to be antigenic or immunogenic.

PMDA accepted the above response.

2.B.(2) Measures to prevent contamination

During the process validation, 1 batch was found to be contaminated with *Staphylococcus epidermidis* on Day [redacted] of cell culture for production. PMDA asked the applicant to explain the cause of the contamination and the measures to prevent the contamination.

The applicant explained as follows:

It seemed that the contamination was caused by leakage of media after the bioreactor was improperly connected to the media container. As a measure to prevent the contamination, the employees were

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retrained on the connecting procedures. Nine batches produced on a commercial manufacturing scale after 2007 were all free of such contamination.

Based on the manufacturing history, PMDA concluded that another contamination of this kind is unlikely to occur in future production and accepted the above response.

2.B.(3) Drug substance specifications

PMDA requested the applicant to include in the drug substance specifications a test intended to detect a structural change without charge variation and to directly assess the consistency of the structure of ustekinumab, including heterogeneity due to post-translational modifications etc.

The applicant responded that peptide mapping will be included in the drug substance specifications in order to assure the consistency of the structure of ustekinumab, including heterogeneity.

PMDA accepted the above response.

2.B.(4) Needle guard fitted to syringe

PMDA asked the applicant to explain the possibility that the needle guard fitted to the syringe is activated improperly during the use of the product.

The applicant responded as follows:

In foreign countries, no adverse events related to product malfunctions have been reported to date. The following malfunction is most likely to occur: the entire prefilled syringe contents have not been injected and as a result, the needle guard is not activated. However, such a malfunction does not cause adverse events to patients or healthcare providers. An illustrated explanation on how to use the needle guard will be included in the package insert, as a guide to healthcare providers.

PMDA accepted the above response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

As the primary pharmacodynamic studies of ustekinumab, the binding of ustekinumab to IL-12 and IL-23, inhibition of IL-12 and IL-23 binding to their receptors, inhibition of IL-12 and IL-23 bioactivity, and species binding and neutralization activity were determined. As the reference data, the results from a study using a murine model of psoriasis were submitted. As the secondary pharmacodynamic studies, its effects on asthma and its cross-reactivity with normal human tissues were studied. Although no safety pharmacology studies have been performed, the effects of ustekinumab on the functions listed in the safety pharmacology core battery were investigated based on the data from 26-week and 4-week repeat-dose toxicity studies in cynomolgus monkeys, in

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accordance with the ICH guidelines. Ustekinumab derived from the cell line B cultured in medium containing bovine fetal serum was used in pharmacology studies, but, in some studies, ustekinumab derived from the cell line C or ustekinumab derived from the cell line D cultured in serum-free medium were used instead. No pharmacodynamic drug interaction studies have been performed.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Binding to human IL-12 and IL-23 (4.2.1.1.1)

3.(i).A.(1).1).(a) Binding to IL-12, IL-23, and IL-12/23p40

The binding of ustekinumab to human IL-12, IL-23, or IL-12/23p40 ([redacted] µg/mL) was determined by ELISA. Ustekinumab was shown to have comparable binding to each of IL-12, IL-23, and IL-12/23p40.

n**3.(i).A.(1).1).(b) Binding to proteins related to IL-12/23p40**

3.(i).A.(1).1).(b) Binding to proteins related to IL-12/23p40

The binding of ustekinumab to the following proteins was determined by dot blotting: IL-12; IL-12/23p40; IL-6; IL-6 receptor (IL-6sR) and ciliary neurotrophic factor receptor (CNTFR), which are structurally related to IL-12/23p40; and the fusion protein of antibody crystallizable fragment (Fc) and IL-11 receptor, which is functionally related to IL-12/23p40 (IL-11R/Fc). Ustekinumab bound to IL-12 and IL-12/23p40, but not to IL-6, IL-6sR, CNTFR, or IL-11R/Fc.

3.(i).A.(1).1).(c) Crystal structure analysis

X-ray crystallographic analysis of ustekinumab Fab/IL-12 complex, formed by the reaction of the antigen-binding fragment (Fab) of ustekinumab with deglycosylated IL-12, showed that the variable domain fragment (Fv) of ustekinumab binds to the epitope in the D1 domain of IL-12/23p40 comprised of three domains (D1-D3), and that the epitope is distant from IL-12p35 (IL-12 consists of IL-12/23p40 and IL-12p35 subunits). The applicant explained that since IL-23p19 overlaps well with IL-12p35 (IL-23 consists of IL-12/23p40 and IL-23p19 subunits) (Beyer BM et al. *J Mol Biol.* 2008;382:942-55), it is believed that also in the case of IL-23, ustekinumab binds to the epitope in the D1 domain of IL-12/23p40 and that the D1 domain is distant from IL-23p19.

3.(i).A.(1).1).(d) Binding epitope analysis

The amino acid residues of IL-12/23p40 involved in the binding to ustekinumab were identified by binding epitope analysis, using protein variants with amino acid residues mutated in the D1 domain. Introduction of mutations using site-directed mutagenesis resulted in reduced binding to ustekinumab, indicating that M23, L40, S43, E45, E59, and D62 are the amino acid residues of IL-12/23p40 involved in the binding to ustekinumab.

3.(i).A.(1).1).(e) Analysis of binding affinity

The equilibrium constants (K_D) for ustekinumab binding to IL-12 and IL-23 as determined by surface plasmon resonance, were [redacted] and [redacted] pmol/L ([redacted] and [redacted] µg/mL), respectively.

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3.(i).A.(1).1).(f) Stoichiometric analysis

The stoichiometry of ustekinumab binding to IL-12 or IL-23 was conducted by isothermal titration calorimetry. Human IL-12 and IL-23 bound to ustekinumab at ratios of 2:0.94 and 2:0.92, respectively, showing the expected ligand to antibody ratio of 2:1.

3.(i).A.(1).2) Inhibition of human IL-12 and IL-23 binding to their receptors (4.2.1.1.2)

3.(i).A.(1).2).(a) Inhibition of binding to IL-12 receptor β-1 (IL-12Rβ1)

Human IL-12 or IL-23 ([redacted] ng/mL each) was reacted with ustekinumab ([redacted] ng/mL), which was added to IL-12Rβ1/Fc fusion protein. Ustekinumab demonstrated equivalent inhibition of IL-12 and IL-23 binding to IL-12Rβ1/Fc.

3.(i).A.(1).2).(b) Inhibition of binding to receptor complexes IL-12Rβ1/β2 and IL-12Rβ1/23R

Human IL-12 or IL-23 was reacted with ustekinumab or anti-IL-12/23p40 mAb (C8.3) that recognizes a different epitope than ustekinumab and that has no neutralization activity, which was added to the IL-12 responsive cell line (H) or the IL-23 responsive cell line (NKL). Ustekinumab inhibited IL-12 and IL-23 from binding to H cells and NKL cells, respectively, whereas IL-12/23p40 mAb with no neutralization activity did not inhibit IL-12 or IL-23 from binding to the cells.

Based on the above, the applicant explained that ustekinumab was shown to inhibit IL-12 and IL-23 from binding to their receptor complexes expressed on the cell membrane.

3.(i).A.(1).2).(c) Binding ability to IL-12 and IL-23 already bound to receptors

Human IL-12 or IL-23 was reacted with H cells or NKL cells and added with ustekinumab or anti-IL-12/23p40 mAb (G) with no neutralization activity. While G was detected on the cell surface, ustekinumab was not detected on the cell surface.

Based on the above, the applicant inferred that ustekinumab cannot bind to IL-12 or IL-23 that is already bound to receptor complexes on the cell surface.

3.(i).A.(1).2).(d) CDC activity

Human peripheral blood lymphocytes (PBL) activated by phytohemagglutinin (PHA) were added with human IL-12 and ustekinumab [redacted] μg/mL and treated with complement. Ustekinumab did not induce CDC of PHA-activated PBL.

3.(i).A.(1).3) Inhibition of IL-12-mediated Th1 cellular response and IL-23-mediated Th17 cellular response (4.2.1.1.3)

3.(i).A.(1).3).(a) Effects on intracellular signaling

The effects of ustekinumab on IL-12-mediated intracellular signaling were determined by flow cytometry. Ustekinumab ([redacted] or [redacted] μg/mL) was reacted with human IL-12 or IL-23 ([redacted] ng/mL each), which was added to NKL cells. Ustekinumab inhibited IL-12-mediated phosphorylation

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of signal transducers and activators of transcription STAT4 and STAT6 and IL-23-mediated phosphorylation of STAT3.

3.(i).A.(1).3).(b) Effects on the expression of cell surface markers

The effects of ustekinumab on IL-12-mediated expression of cell surface markers were determined by flow cytometry. Human IL-12 ([redacted] ng/mL) was reacted with PHA-activated human peripheral blood mononuclear cells and added with ustekinumab (derived from the cell line B) [redacted] μg/mL. Ustekinumab inhibited the otherwise increased IL-12-mediated expression of IL-12 receptor β-2 (IL-12Rβ2) and cutaneous lymphocyte antigen (CLA).

3.(i).A.(1).3).(c) Effects on cytokine production

The effects of ustekinumab on IL-12-mediated cytokine production were determined by ELISA. Ustekinumab (derived from the cell line C) or ustekinumab Fab ([redacted] nmol/L) was reacted with human IL-12 ([redacted] ng/mL), which was added to PHA-activated human T cell blasts. Both ustekinumab and ustekinumab Fab inhibited IFN-γ mRNA expression.

The effects of ustekinumab on IL-23-mediated cytokine production were determined by ELISA. [redacted]

When ustekinumab ([redacted] μg/mL) and human IL-23 ([redacted] ng/mL) were added to NKL cells and incubated in the presence of IL-2 and anti-IFN-γ antibodies, ustekinumab inhibited the production of IL-10.

3.(i).A.(1).4) Species binding and neutralization activity (4.2.1.1.4)

3.(i).A.(1).4).(a) Neutralization activity against IL-12 and IL-23 from different species

The neutralization activity of ustekinumab against IL-12 and IL-23 from different species was determined by ELISA and RT-PCR. Cytokine-containing culture supernatants prepared from adherent cells in the peripheral blood mononuclear cells or splenocytes from humans, chimpanzees, baboons, cynomolgus monkeys, marmosets, rhesus monkeys, dogs, rabbits, rats, and mice, and serially diluted ustekinumab solutions were added to PHA-activated T cells of the respective species, and IL-12-mediated IFN-γ mRNA expression and IFN-γ protein production and IL-23-mediated IL-17A protein production were used as measures of neutralization activity. Ustekinumab neutralized human, chimpanzee, baboon, cynomolgus monkey, marmoset, and rhesus monkey IL-12, but showed little activity to dog and rabbit IL-12 and no activity to rat and mouse IL-12. Ustekinumab neutralized human, chimpanzee, baboon, cynomolgus monkey, and rhesus monkey IL-23, but showed partial activity to dog IL-23 and no activity to rat and mouse IL-23.

3.(i).A.(1).4).(b) Binding to and neutralization activity against recombinant cynomolgus monkey IL-12 and IL-23

Recombinant cynomolgus monkey IL-12 or IL-23 was added with ustekinumab. Ustekinumab was

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shown to have comparable binding to human and cynomolgus monkey IL-12 and IL-23. [redacted].

Ustekinumab derived from the cell line C and that from the cell line D were compared for their neutralization activity against recombinant cynomolgus monkey IL-12. They showed comparable inhibition of cynomolgus monkey IL-12 ([redacted] ng/mL)-mediated IFN-γ production from H cells.

3.(i).A.(1).4).(c) Neutralization activities of anti-mouse IL-12/23p40 antibody and ustekinumab against mouse IL-12 and IL-23

[redacted].

3.(i).A.(1).5) Effects in a murine model of psoriasis (Reference data 4.2.1.1.5)

Psoriasis-like symptoms were induced in severe combined immunodeficiency (SCID) mice (n = 10/group) by intraperitoneal transfer of $CD4^{+}CD45RB^{hi}CD25^{-}$ cells isolated from BALB/cBy mouse splenocytes and 7 and 35 days after the cell transfer, the mice were treated intraperitoneally with 0.5 mg of anti-mouse IL-12/23p40 antibody. Compared to the negative control antibody, anti-mouse IL-12/23p40 antibody significantly reduced the mean severity score, reduced acanthosis and rete ridges (downgrowth to the basal layer), and inhibited inflammatory cell infiltration, and significantly reduced the expression of IL-23p19, IL-1α, IL-6, IL-17A, IL-17F, and IL-22 mRNA and tended to reduce the expression of IFN-γ, TNF-α, and IL-12p35 mRNA in skin tissues.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Effects of ustekinumab in a model of asthma in cynomolgus monkeys (a pilot study) (4.2.1.2.2)

In a model of asthma in cynomolgus monkeys, the effects of IL-12 inhibition by ustekinumab on the exacerbation of asthma were studied. Cynomolgus monkeys (n = 2/group) with positive bronchoconstrictor responses to inhaled *Ascaris suum* antigen were intravenously given ustekinumab (9 or 45 mg/kg) 3 weeks later and then challenged with the antigen 1 hour later. Compared to the changes following the initial antigen challenge before ustekinumab treatment, ustekinumab did not affect pulmonary resistance, dynamic compliance, or cellular composition in bronchoalveolar lavage fluid (BALF). At 4 weeks after the first dose, 1 of the cynomolgus monkeys treated with ustekinumab at 45 mg/kg was given the same dose of ustekinumab followed by antigen challenge in the same manner. As a result, an increased bronchoconstrictor response and an increase in eosinophil count in the BALF were observed.

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3.(i).A.(2).2) Effects of ustekinumab in a model of asthma in cynomolgus monkeys (a confirmatory study) (4.2.1.2.3)

Cynomolgus monkeys (n = 4/group) with positive bronchoconstrictor responses to *Ascaris suum* antigen were given ustekinumab at 45 mg/kg prior to antigen challenge on two occasions, in the same manner as in the pilot study. Compared to the changes following the initial antigen challenge before ustekinumab treatment, administration of ustekinumab on two occasions did not affect the bronchoconstrictor response or eosinophil count in the BALF following antigen challenge.

3.(i).A.(2).3) Cross-reactivity with normal human tissues (4.2.1.2.4)

Using cryosections of normal human tissues[3], cross-reactivity of ustekinumab with normal human tissues was studied by immunohistochemical staining. Ustekinumab did not cross-react with any of the normal human tissues tested.

3.(i).B Outline of the review by PMDA

PMDA asked the applicant to sort out the latest findings on the association between psoriasis and IL-12/IL-23, and the data from non-clinical and clinical studies of ustekinumab, etc. and to discuss in details the mechanism of action of ustekinumab in the treatment of psoriasis.

The applicant explained as follows:

(a) The activation of Th1 and Th17 cells by IL-12 and IL-23, respectively, is believed to play a key role in the development of psoriasis (Nestle FO, Conrad C. *J Invest Dermatol* 2004;123:xiv-xv, Lew W, Bowcock AM, Krueger JG. *Trends Immunol.* 2004;25:295-305, Nickoloff BJ. *Nat Med.* 2007;13:242-4), (b) IL-12 is believed to promote induction of differentiation from $CD4^+$naïve T cells to Th1 cells and activation of natural killer (NK) cells, production of cytokines such as IFN-γ from Th1 and NK cells, and the expression of CLA in inflammatory sites and thereby induces accumulation of T cells in skin lesions of psoriasis and epithelial cell proliferation, leading to the exacerbation of psoriasis (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68), (c) IL-23 induces the production of cytokines such as IL-17 and IL-22 from Th17 cells and these cytokines are believed to induce psoriatic lesions such as epidermal thickening (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68, Zheng Y et al. *Nature.* 2007;445:648-51), (d) Increased expressions of IL-12 and IL-23 genes and proteins in the lesional skin and serum of patients with psoriasis have been reported (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68, Roussaki-Schulze AV et al. *Int J Clin Pharmacol Res*. 2005;xxv:169-73, Chan JR et al. *J Exp Med*. 2006;203:2577-87) and psoriasis therapies such as cyclosporine, narrow-band UVB phototherapy, and anti-TNF therapy have been found to regulate the levels of IL-12 and IL-23 (Torti DC, Feldman SR. *J Am Acad Dermatol*. 2007;57:1059-68), and (e) Single-nucleotide polymorphisms in the IL-12B gene encoding the IL-12/23p40 subunit and the gene encoding the IL-23 receptor subunit have been identified to be associated with psoriasis susceptibility (Cargill M et al. *Am J Hum Genet*. 2007;80:273-90). Taking

[3] Including all normal human tissues as recommended in "Points to Consider in the Manufacture and Testing of Monoclonal Products for Human Use (FDA/CBER)".

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account of these findings, IL-12 and IL-23 are considered to play a very important role in the pathogenesis of psoriasis.

As Foreign Study C0379T01 showed that mRNA expression levels of cytokines produced by activated Th1 cells were reduced in psoriatic skin lesions in patients treated with ustekinumab (Toichi E, et al. *J Immunol*. 2006;177:4917-26), it is inferred that the activation of Th1 and Th17 cells is inhibited *in vivo* as well and it is discussed that ustekinumab inhibits the activation of Th1 and Th17 cells by IL-12 and IL-23, respectively, in the psoriatic skin lesions and draining lymph nodes as observed *in vitro* and exerts its therapeutic effects through the reduction of the expression of cytokines, chemokines, and adhesion molecules etc. involved in the pathogenesis of psoriasis.

Based on the submitted data and responses etc., PMDA concluded that the pharmacological effects of ustekinumab via IL-12/23p40 have been demonstrated and that ustekinumab can be expected to be effective in the treatment of psoriasis.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The pharmacokinetics of ustekinumab administered subcutaneously or intravenously were investigated in cynomolgus monkeys. Ustekinumab concentrations in the serum and milk were determined by enzyme-linked immunosorbent assay (ELISA) with human IL-12 adsorbed onto the plate and electrochemiluminescent immunoassay (ECLIA) using monoclonal antibodies against the variable region of ustekinumab (lower limit of quantification, 0.09-0.17 μg/mL [ELISA]; 0.09 μg/mL [ECLIA]), respectively. Anti-ustekinumab antibodies were detemined by ELISA. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean ± standard deviation (SD).

3.(ii).A.(1) Absorption

3.(ii).A.(1).1 Single-dose studies (4.2.2.2.1 to 4.2.2.2.2)

The pharmacokinetic parameters after a single subcutaneous or intravenous administration of ustekinumab in male cynomolgus monkeys were as shown in Table 7. The bioavailability of subcutaneous ustekinumab was estimated to be ≥90% by comparison of the AUC_∞ values of single-dose subcutaneous and intravenous studies using the same dose of ustekinumab.

Table 7. Pharmacokinetic parameters of ustekinumab after single-dose administration to cynomolgus monkeys

Dose (mg/kg)	Route	n	C_{max} (μg/mL)	t_{max} (day)	AUC_∞ (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	Vd_z (mL/kg)
0.9	s.c.	3	8.16 ± 1.69	3 (3-7)	131.18 ± 86.00	4.71 ± 4.67	-	-
0.9	i.v.	3	25.57 ± 5.80	-	138.24 ± 27.02	7.58 ± 1.68	6.7 ± 1.5	70.1 ± 19.0
9	i.v.	3	436.50 ± 48.36	-	2452.50 ± 396.54	12.10 ± 1.33	3.7 ± 0.6	60.4 ± 13.2

Mean ± SD except for t_{max}, Median (Min-Max) for t_{max}, C_{max}: maximum serum concentration, t_{max}: time to reach the maximum serum concentration,
AUC_∞: area under the serum concentration-time curve from time zero to infinite time, $t_{1/2}$: elimination half-life, CL: total body clearance, Vd_z: volume of distribution at the terminal phase

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3.(ii).A.(1).2) Repeat-dose studies (4.2.3.6.1, 4.2.3.5.1.1, 4.2.3.2.1)

Male and female cynomolgus monkeys (n = 2/sex) were subcutaneously administered 45 mg/kg of ustekinumab twice weekly for 3 weeks. The trough serum concentration of ustekinumab increased with each dose. The C_{max} after the first dose was 349.29 ± 32.51 μg/mL and the C_{max} after the last (the 6th) dose was 2460.02 ± 649.57 μg/mL and ustekinumab was eliminated with a $t_{1/2}$ of 16.31 ± 6.62 days after the last dose.

Male cynomolgus monkeys (n = 6/group) were subcutaneously administered 22.5 or 45 mg/kg of ustekinumab twice weekly for 13 weeks. The C_{max} values after the first dose were 262.57 ± 57.37 and 387.72 ± 111.96 μg/mL, respectively, the C_{max} values after the last (the 26th) dose were 2598.54 ± 702.50 and 3781.85 ± 1322.19 μg/mL, respectively, and ustekinumab was eliminated with a $t_{1/2}$ of 19.88 to 21.93 days (median) after the last dose. The AUCs from time 0 to 91 days after the last dose were 65,174.02 ± 34,807.11 and 86,668.58 ± 37,837.40 μg·day/mL, respectively.

Male and female cynomolgus monkeys (n = 8/sex/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly for 26 weeks. The C_{max} values after the first dose were 370.11 ± 197.51 and 672.64 ± 366.79 μg/mL, respectively, the AUCs from time 0 to 3 days after administration (AUC_{3day}) were 765.25 ± 436.75 and 1424.23 ± 700.72 μg·day/mL, respectively, the C_{max} values after the last (the 52nd) dose were 1419.13 ± 493.65 and 2347.08 ± 660.48 μg/mL, respectively, and the AUC_{3day} values were 3660.79 ± 1060.79 and 6185.90 ± 1500.47 μg·day/mL, respectively, and ustekinumab was eliminated with $t_{1/2}$ values of 13.27 ± 4.30 and 11.60 ± 1.95 days, respectively, after the last dose. Trough serum concentrations of ustekinumab were constant after Day 71, which demonstrated that steady-state is reached by Week 13.

The C_{max} and AUC_{∞} values after a single subcutaneous dose of ustekinumab and after the first dose in a subcutaneous repeat-dose study increased in an almost dose-proportional manner.

The applicant explained about a longer $t_{1/2}$ after multiple-dose administration compared to single-dose administration as follows:

It is inferred that the clearance observed after single-dose administration was accelerated due to the development of anti-ustekinumab antibodies. The $t_{1/2}$ was not substantially different between single- and multiple-dose administrations, and there should be no possibility of higher accumulation of ustekinumab after multiple dosing than predicted from that after single-dose administration.

3.(ii).A.(1).3) Comparability studies (4.2.2.2.3 to 4.2.2.2.4)

As two different ustekinumab-producing cell lines (B and D) and two different formulations (liquid and lyophilized formulations) were used during pharmaceutical development, single-dose studies in monkeys were conducted to evaluate the comparability of the pharmacokinetic profile of ustekinumab between batches of material produced by the two different cell lines and between the two different formulations.

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Male cynomolgus monkeys (n = 12/group) received a single subcutaneous dose of 9 mg/kg of ustekinumab derived from the cell line B or D. The C_{max} (98.08 ± 22.59 and 82.17 ± 13.75 μg/mL, respectively) and AUC_{∞} (2377.71 ± 718.07 and 2226.15 ± 688.33 μg·day/mL, respectively) were comparable between the two groups and the t_{max}, $t_{1/2}$, CL/F, Vd_z/F, and MRT were also comparable.

Male cynomolgus monkeys (n = 15/group) received a single intravenous dose of 4.5 mg/kg of a lyophilized or liquid formulation of ustekinumab and the C_{max} (49.12 ± 24.25 and 45.30 ± 19.74 μg/mL, respectively) and AUC_{∞} (764.90 ± 233.99 and 792.16 ± 195.94 μg·day/mL, respectively) were comparable between the two groups and the $t_{1/2}$, CL, and Vd_z were also comparable.

3.(ii).A.(2) Distribution

No distribution studies of ustekinumab have been conducted because ustekinumab is a fully human IgG monoclonal antibody and generally, cellular uptake of a biological macromolecular drug is not high and the tissue distribution of ustekinumab is considered limited based on its volume of distribution, target proteins, and cross-reactivity with normal human tissues, etc. Fetal transfer studies were conducted using unlabeled ustekinumab.

3.(ii).A.(2).1) Fetal transfer (4.2.3.5.2.1 to 4.2.3.5.2.2)

Pregnant cynomolgus monkeys (n = 12/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to gestation day 51. The maternal serum ustekinumab concentrations on gestation days 100 to 102 were 45.24 ± 37.30 and 55.65 ± 16.63 μg/mL, respectively, and the fetal serum ustekinumab concentrations were 16.56 ± 12.32 and 21.56 ± 10.22 μg/mL, respectively.

Pregnant cynomolgus monkeys (n = 12/group) were intravenously given 9 or 45 mg/kg of ustekinumab once weekly from gestation day 20 to gestation day 48. The maternal serum ustekinumab concentrations on gestation day 100 were 19.13 ± 9.47 and 54.47 ± 31.13 μg/mL, respectively, and the fetal serum ustekinumab concentrations were 8.39 ± 4.29 and 19.14 ± 10.64 μg/mL, respectively.

3.(ii).A.(3) Metabolism and excretion

No metabolism and excretion studies of ustekinumab have been conducted because ustekinumab is a fully human IgG monoclonal antibody and is degraded into peptides and amino acids and excreted or recycled via pathways in the same manner as endogenous IgG in humans. A study of excretion into milk was conducted.

3.(ii).A.(3).1) Excretion into milk (4.2.3.5.3.1)

Pregnant cynomolgus monkeys (n = 20/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to lactation day 33. The ustekinumab concentrations in milk on lactation day 14 (2 days after administration) were 1.43 ± 0.45 and 3.12 ± 1.66 μg/mL,

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respectively, and the ustekinumab concentrations in milk on lactation day 28 (2 days after administration) were 1.64 ± 0.48 and 3.18 ± 1.71 μg/mL, respectively.

3.(ii).B Outline of the review by PMDA

PMDA asked the applicant to explain the relationship of IL-12 and IL-23 with the expression of cytochrome p450 (CYP) enzymes.

The applicant explained as follows:
Although there has so far been no report that IL-12/23 affects CYP enzyme expression, some cytokines such as IL-6 and IL-1β have been reported to down-regulate the expression of various CYPs (Abdel-Razzak Z et al. *Mol Pharmacol*. 1993;44: 707-15), and the relationship between IL-12/23 and CYP cannot be denied, nor are there data regarding ustekinumab interactions with drugs that are metabolized by CYP enzymes. Thus, an *in vitro* study to determine the effect of IL-12/23 on CYP enzyme expression is currently ongoing.

PMDA considers as follows:
As it is also envisaged that ustekinumab will be used in combination with CYP substrates such as cyclosporine for the treatment of psoriasis, it is necessary to complete the above study as soon as possible and appropriately provide the obtained information to healthcare providers in clinical settings.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of ustekinumab conducted were repeat-dose toxicity, reproductive and developmental toxicity, and local tolerance studies. Safety pharmacology endpoints and immunotoxicity measurements were incorporated in the toxicity studies. No anti-ustekinumab antibodies were detected in the animals used in the toxicity studies and ustekinumab exposure has been confirmed to be maintained during the dosing period in all studies.

3.(iii).A.(1) Single-dose toxicity (4.2.2.2.1 to 4.2.2.2.2, 4.2.3.2.1)

No single-dose toxicity studies have been conducted. Single-dose toxicity was evaluated based on the data from single subcutaneous dose and single intravenous dose pharmacokinetic studies in cynomolgus monkeys (4.2.2.2.1 to 4.2.2.2.2) and the data after the first dose in a 26-week subcutaneous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.1). No mortality occurred and no ustekinumab-related effects were observed for clinical observations, body weight, or food consumption up to the high dose of 9 mg/kg in the pharmacokinetic studies and up to the high dose of 45 mg/kg in the 26-week subcutaneous repeat-dose toxicity study (observation after the first dose).

3.(iii).A.(2) Repeat-dose toxicity

As repeat-dose toxicity studies, a 26-week subcutaneous dose toxicity study and a 4-week intravenous dose toxicity study in cynomolgus monkeys were conducted. In the 26-week subcutaneous dose

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toxicity study, an animal in the high dose group had diarrhoea, body weight loss, and elevated white blood cell count, etc., which were considered to be associated with bacterial enteritis, were observed and their relationship to ustekinumab could not be denied. The AUC_{72h} and C_{max} of ustekinumab (after the last dose) at the no-observed-adverse-effect level (NOAEL) (45 mg/kg) in the 26-week subcutaneous dose toxicity study in cynomolgus monkeys were approximately 22-fold the AUC_{∞} after single-dose administration and approximately 116-fold the C_{max} after 4 weeks of once-weekly subcutaneous administration (after the 4th dose) to humans at the maximum recommended clinical dose of 90 mg in a foreign phase II study (Study C0379T04).[4]

3.(iii).A.(2).1) Twenty-six-week subcutaneous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.1)

Cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly for 13 or 26 weeks. In this study, as immunological tests, peripheral blood lymphocyte subset analyses ($CD2^+$, $CD3^-$, $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD14^+$, $CD16^+$, $CD20^+$, $CD45^+$) were performed and anti-keyhole limpet hemocyanin (KLH) antibody response was measured following intramuscular injection of KLH in incomplete Freund's adjuvant on Days 14 and 30. One of 16 animals in the 22.5 mg/kg group had ventricular extrasystoles, which were considered coincidental and unrelated to ustekinumab. At Week 26, 1 of 16 animals in the 45 mg/kg group had diarrhoea, body weight loss, and elevated white blood cell count and hyperplasia of the myeloid cells and acute inflammation in the ileum, which were considered to be associated with bacterial enteritis. Although their relationship to inhibition of IL-12 and IL-23 by ustekinumab could not be denied, no findings indicative of immunotoxicity were observed in this animal and immunosuppression by ustekinumab was not suggested in the other dose group or other toxicity studies. Thus, bacterial enteritis may have been coincidental. In the immunological test, peripheral blood lymphocyte subset analyses showed changes in the percentages of $CD45^+$, $CD16^+$, and $CD2^+$ in animals treated with ustekinumab, but these changes were small and were not considered of toxicological significance. KLH analysis showed that anti-KLH antibody titers for male animals in the 45 mg/kg group tended to decrease, which was not considered of toxicological significance because this finding occurred in males only and animal to animal variation in anti-KLH antibody response was observed. The NOAEL was determined to be 45 mg/kg. Safety pharmacology evaluations revealed no ustekinumab-related effects on the cardiovascular, central nervous, or respiratory system.

3.(iii).A.(2).2) Four-week intravenous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.3)

Cynomolgus monkeys were intravenously given 0 (saline), 9, or 45 mg/kg of ustekinumab once weekly for 4 weeks. In the 45 mg/kg group, 1 of 10 animals had ventricular extrasystoles and on Day

[4] The AUC or C_{max} of ustekinumab administered at the proposed dosage regimen in Japanese patients with psoriasis was not calculated. The trough concentration at the NOAEL (45 mg/kg) in a 26-week subcutaneous dose toxicity study in cynomolgus monkeys after the last dose (Day 166) was 531-fold (maximum) or 2125-fold (median) the trough concentration at Week 64 in Japanese patients with psoriasis administered ustekinumab at the maximum recommended clinical dose of 90 mg at Weeks 0 and 4 and then every 12 weeks (Study JPN-02).

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28 (6 days after the 4th dose), compared to the control group, its relative lymphocyte counts decreased and its absolute and relative neutrophil counts increased. The ventricular extrasystoles were considered coincidental and unrelated to ustekinumab. When the lymphocyte and neutrophil values, etc., were compared with their pre-dose values, only 1 of the 10 animals showed a marked decrease in relative lymphocyte counts and a marked increase in relative neutrophil counts, and lymphocyte and neutrophil values for the other animals were almost unchanged from their pre-dose values. The lymphocytes or neutrophils on Days 9 and 58 were unaffected and moreover, no changes were observed in males. Therefore, these changes were not considered of toxicological significance. There were no ustekinumab-related effects on other parameters including immunotoxicity endpoints. The NOAEL in this study was determined to be 45 mg/kg. Safety pharmacology evaluations revealed no ustekinumab-related effects on the cardiovascular, central nervous, or respiratory system.

3.(iii).A.(3) Genotoxicity

Since ustekinumab is an antibody drug and there should be little concern about genotoxicity, no genotoxicity studies have been conducted.

3.(iii).A.(4) Carcinogenicity

Ustekinumab does not neutralize IL-12 or IL-23 from mice or rats, which are commonly used in carcinogenicity studies, and although anti-mouse IL-12/23p40 antibody (CNTO 3913), an antibody analogous to ustekinumab, neutralizes mouse IL-12 and IL-23, the information to be obtained from a carcinogenicity study with CNTO 3913 should be limited. Therefore, no carcinogenicity studies using ustekinumab or the antibody analogous to ustekinumab have been performed.

3.(iii).A.(5) Reproductive and developmental toxicity

A male fertility study in cynomolgus monkeys, a female fertility study with an analogous antibody CNTO 3913 in mice, an embryo-fetal development study in cynomolgus monkeys, and a study for effects on pre- and postnatal development including maternal function in cynomolgus monkeys were conducted by the subcutaneous route of administration. An embryo-fetal development study in cynomolgus monkeys was conducted by the intravenous route of administration. Ustekinumab was not teratogenic and there were no effects on either male or female fertility, parturition, embryo-fetal development, or offspring development in any of the studies. Ustekinumab has been shown to cross the placenta (4.2.3.5.2.1) and be excreted in milk (4.2.3.5.3.1) in cynomolgus monkeys [see "3.(ii).A.(2).1) and 3.(ii).A.(3).1)"].

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation

The levels of IL-12 in seminal plasma of infertile men were lower than those of fertile men and there was significant correlation between the IL-12 levels and the total sperm count and percentage of morphologically normal sperm in the semen (Naz RK et al. *J Androl*. 1998;19:302-307). Thus, a male fertility study in cynomolgus monkeys was conducted.

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3.(iii).A.(5).1).(a) Male fertility study in cynomolgus monkeys (4.2.3.5.1.1)

Male cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly for 13 weeks (9 weeks prior to mating and 4 weeks of mating period). There were no ustekinumab-related effects on clinical observations, body weight and food consumption, semen analysis, mating behavior, or serum testosterone and inhibin B levels. No anti-ustekinumab antibodies were detected. The NOAEL for general and reproductive toxicity was determined to be 45 mg/kg.

3.(iii).A.(5).1).(b) Female fertility study with CNTO 3913 in mice (4.2.3.5.1.2)

Female mice were subcutaneously administered 0 (phosphate-buffered saline), 5, or 50 mg/kg of CNTO 3913 (anti-mouse IL-12/23p40 antibody) or 50 mg/kg of an isotype-matched control monoclonal antibody (CNTO 1322) as the negative control article of CNTO 3913, twice weekly beginning 15 days before mating and continuing through gestation day 7. Cesarean section was performed on gestation day 13 and female fertility was evaluated. Although 1 of 25 dams in the CNTO 3913 50 mg/kg group had total litter loss, as the litter average for nonviable embryos in the CNTO 3913 50 mg/kg group (0.3) was lower than those in the vehicle control (0.8) and negative control article (0.7) groups, the finding was not considered related to CNTO 3913. The NOAEL for general and reproductive toxicity was determined to be 50 mg/kg.

3.(iii).A.(5).2) Embryo-fetal development studies

3.(iii).A.(5).2).(a) Subcutaneous administration study in cynomolgus monkeys (4.2.3.5.2.1)

Pregnant cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to gestation day 51. Hormone concentrations in maternal and fetal serum were measured and as immunological tests, maternal and fetal peripheral blood lymphocyte subset analyses and immunohistochemical analysis of fetal lymphoid tissue were performed. Abortion occurred in 1 of 12 dams in the control group, abortion occurred in 3 of 12 dams and embryo/fetal death occurred in 2 of 12 dams in the 22.5 mg/kg group, and embryo/fetal death occurred in 2 of 12 dams in the 45 mg/kg group. Although the incidence of abortion or embryo/fetal death in the 22.5 mg/kg group (5 of 12 dams, 41.7%) exceeded the laboratory historical control range (mean 8.2%, maximum 20%), the incidence in the 45 mg/kg group (2 of 12 dams, 16.7%) was within the historical control range and no dose-dependency was observed. Abortion or embryo/fetal death did not necessarily occur in animals with high ustekinumab exposure levels. There was no correlation between individual exposure levels and abortion or embryo/fetal death. In addition, an embryo-fetal development study in cynomolgus monkeys by intravenous administration (4.2.3.5.2.2) showed that the incidence of abortion or embryo/fetal death in animals treated with ustekinumab was within the historical control range. Therefore, the findings were not considered related to ustekinumab. Although statistically significant differences between the ustekinumab and control groups were observed for serum hormone concentrations (progesterone, 17β-estradiol, prolactin), these changes were within the laboratory historical control range or transient. There was no relationship between changes in serum hormone concentrations and abortion or embryo/fetal death, and maintenance of pregnancy was not affected. Therefore, these changes were not considered related to ustekinumab.

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Asymmetrically aligned palatal rugae were observed in 1 of 7 fetuses in the 22.5 mg/kg group and 1 of 10 fetuses in the 45 mg/kg group, but were not reported in a study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1) and morphological changes in the palate are commonly observed in adult cynomolgus monkeys and are not associated with dysfunction. Thus, this finding was not considered of toxicological significance. No anti-ustekinumab antibodies were detected in maternal or fetal serum. The NOAEL for maternal and embryo-fetal toxicity was determined to be 45 mg/kg.

3.(iii).A.(5).2).(b) Intravenous administration study in cynomolgus monkeys (4.2.3.5.2.2)

Pregnant cynomolgus monkeys were intravenously given 0 (saline), 9, or 45 mg/kg of ustekinumab once weekly from gestation day 20 to gestation day 48. As immunological tests, maternal and fetal peripheral blood lymphocyte subset analyses and immunohistochemical analysis of fetal lymphoid tissue were also performed. Abortion occurred in 1 of 12 dams each in the 9 mg/kg and 45 mg/kg groups, which was not considered related to ustekinumab because abortion occurred in 1 of 12 dams and embryo/fetal death occurred in 1 of 12 dams also in the control group and the incidence was within the laboratory historical control range (mean 8.2%, maximum 20%), etc.

Asymmetrically aligned palatal rugae were observed in 1 of 11 fetuses in the 9 mg/kg group, but not in the 45 mg/kg group, showing no dose-dependency and this finding was not reported in a study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1) and morphological changes in the palate are commonly observed in adult cynomolgus monkeys and are not associated with dysfunction. Thus, the finding was not considered of toxicological significance. No anti-ustekinumab antibodies were detected in maternal or fetal serum. The NOAEL for maternal and embryo-fetal toxicity was determined to be 45 mg/kg.

3.(iii).A.(5).3) Study for effects on pre- and postnatal development, including maternal function in cynomolgus monkeys (4.2.3.5.3.1)

Pregnant cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly from gestation day 20 through Day 33 after delivery. In the F1 generation, as immunological tests, peripheral blood lymphocyte subset analyses were performed and immunological development was evaluated (measurement of anti-KLH and anti-tetanus toxoid antibodies). In the 22.5 mg/kg group, abortion occurred in 3 of 20 dams, stillbirth occurred in 2 of 20 dams, and fetal death occurred in 1 of 20 dams. In the 45 mg/kg group, abortion occurred in 3 of 20 dams, stillbirth occurred in 1 of 20 dams, and fetal death occurred in 1 of 20 dams. Also in the control group, abortion occurred in 2 of 20 dams and stillbirth occurred in 3 of 20 dams. As there were no differences in incidence between the control and ustekinumab groups, the findings were not considered related to ustekinumab. Necropsies of the stillbirths revealed no macroscopic abnormalities. In the F1 generation, 1 of 16 animals in the 22.5 mg/kg group died on postnatal day 6 and this animal had low body weight, emaciation, and smaller thymus with an almost empty gastrointestinal tract, but

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no death occurred in the 45 mg/kg group and the incidence of neonatal deaths was within the laboratory historical control range (3.7%). Thus, the death was not considered related to ustekinumab. Although 1 of 16 F1 animals in the 45 mg/kg group was sacrificed moribund on Day 1 after birth due to lateral position and the fingertips bitten off by the dam, the tip of the tail of 1 of 18 F1 animals was bitten off by the dam on Day 17 after birth also in the control group. Thus, the finding was not considered related to ustekinumab. In the F1 generation, there were no ustekinumab-related effects including those on immunological test results. In the ustekinumab groups, ustekinumab was present in the offspring and in the breast milk from lactating dams. No anti-ustekinumab antibodies were detected in maternal or offspring serum. The NOAEL for maternal and offspring toxicity was determined to be 45 mg/kg.

3.(iii).A.(6) Local tolerance study in cynomolgus monkeys (4.2.3.6.1)

Cynomolgus monkeys were subcutaneously given 0 (vehicle, [redacted]% sucrose, [redacted]% mol/L sodium phosphate, [redacted]% polysorbate 80) or 45 mg/kg of ustekinumab or 3 mg/kg of intravenous immunoglobulin (IGIV) as the positive control article, twice weekly for 3 weeks. Animals in the ustekinumab and vehicle control groups had minimal to mild edema at the injection site, which resolved within 48 hours after injection and no histopathological findings were observed. It was concluded that local tolerance of subcutaneous injection of ustekinumab is good.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Carcinogenicity

PMDA asked the applicant to explain the carcinogenic risk of ustekinumab and the risk of exacerbation of malignancy.

The applicant explained as follows:

No tumors or preneoplastic lesions were observed in a 26-week subcutaneous dose toxicity study in cynomolgus monkeys (4.2.3.2.1), suggesting no risk of malignancy development with ustekinumab. As for IL-12/23p40, the target molecule of ustekinumab, however, the anti-tumor effect of IL-12 in laboratory animals has been suggested (Brunda MJ et al. *J Exp Med.* 1993;178:1223-1230, Lee JC et al. *Cancer Res.* 2002;62:747-755) and studies using knockout mice and anti-IL-12/23p40 antibody have suggested the exacerbation of malignancy (Langowski JL et al. *Nature.* 2006;442:461-465). Concerning the risk of photocarcinogenicity, there is a report suggesting the exacerbation of UV-induced skin tumors in IL-12/23p40 knockout mice (Maeda A et al. *Cancer Res.* 2006;66:2962-2969). In addition, the possibility that other immunosuppressive biologics and immunosuppressants are associated with the development of malignancies such as lymphoma in a clinical setting cannot be denied. Taking account of these findings, the risk of malignancy development with ustekinumab also cannot be denied.

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3.(iii).B.(2) Risk of immunosuppression

Concerning the findings considered to be associated with bacterial enteritis observed in 1 of 16 cynomolgus monkeys in the 45 mg/kg group in a 26-week toxicity study (4.2.3.2.1), PMDA asked the applicant to explain their relationship to the immunosuppressive effect of ustekinumab and the risk of infections associated with ustekinumab in humans.

The applicant explained as follows:

Although this animal had inflammatory response, immunohistochemical analysis of lymphoid tissue and peripheral blood lymphocyte subset analyses revealed no findings indicative of immunotoxicity and T-cell dependent anti-KLH antibody response was not affected either. Therefore, the applicant considered that there were no effects on the immune function and that an increased susceptibility to infections was not suggested. Moreover, in repeat-dose toxicity (4.2.3.2.1 and 4.2.3.2.3) and reproductive and developmental toxicity (4.2.3.5.2.1 to 4.2.3.5.2.2) studies in cynomolgus monkeys, the results of immunotoxicity evaluations showed that ustekinumab was not associated with immunosuppression and naturally occurring diarrhoea is often observed in cynomolgus monkeys in the control group or during acclimatization as well (Trib GW et al. *Lab Anim*. 1983;17:65-69). Taking account of these findings, bacterial enteritis may have been coincidental and although its relationship to ustekinumab cannot be denied, it is very unlikely to be related to the immunosuppressive effect of ustekinumab.

In patients genetically deficient in factors involved in Th1/Th17 cell activation, such as IL-12/23p40, IL-12Rβ1, IFN-γ receptors 1 and 2, STAT1, and NEMO (NF-κB essential modulator), an increased susceptibility to initial mycobacterial infection and recurrent *Salmonella* infection has been reported (Novelli F et al. *Cytokine Growth Factor Rev.* 2004;15:367-377, Fieschi C et al. *J Exp Med*. 2003;197:527-535, Fieschi C, Casanova JL. *Eur J Immunol*, 2003;33:1461-1464, Filipe-Santos O et al. *Semin Immunol,* 2006;18:347-361), while reports of other infections are limited. Thus, it is inferred that protective immunity against most microorganisms is maintained during treatment with ustekinumab. However, as serious infections have been reported in Japanese and foreign clinical studies [see "4.(ii) Summary of clinical efficacy and safety"], the risk of infections associated with ustekinumab cannot be denied, as in the case of other immunosuppressive biologics.

3.(iii).B.(3) Cardiac effects

Ventricular extrasystoles were observed in 26-week and 4-week toxicity studies in cynomolgus monkeys (4.2.3.2.1 and 4.2.3.2.3). PMDA asked the applicant to explain its relationship to ustekinumab.

The applicant explained as follows:

It has been reported that ventricular extrasystoles were observed in ECG from 5 of 62 normal cynomolgus monkeys (8%) (Medcallum GE et al. *Am J Vet Res.* 1993;54:327-332) and according to reports on ECGs recorded in cynomolgus monkey toxicity studies (Detweiler DK,

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Electrocardiography in toxicology studies. In: Sipes IG, McQueen CA, Gandolfi AJ ed. *Comprehensive toxicology,* UK: Elsevier Science; 1997;95-115), the incidence of arrhythmia and conductance abnormalities in cynomolgus monkeys (n = 4822) was 2.43% (ventricular extrasystoles, 1.24%; right bundle branch block, 1.12%) and compared to these data, the incidence of ventricular extrasystoles in the ustekinumab toxicity studies was not markedly higher. Furthermore, histopathological examination revealed no toxicological findings in cardiac tissue in these toxicity studies, and in a study of cross-reactivity with normal human tissues (4.2.1.2.4), ustekinumab binding to cardiac tissue was not observed and ustekinumab is not thought to induce antibody or CDC of cardiac cells. Therefore, the ventricular extrasystoles observed in these toxicity studies are not considered related to ustekinumab.

PMDA largely accepts the above responses from a toxicological point of view, but considers that the risk of carcinogenicity and infections due to immunosuppression cannot be denied in view of the pharmacological effects of ustekinumab and it is necessary to carefully assess the safety of ustekinumab in clinical use based on clinical study data and post-marketing data etc.

4. Clinical data

4.(i) Summary of clinical pharmacology studies

4.(i).A Summary of the submitted data

As the evaluation data on the pharmacokinetics of ustekinumab, the results from a phase I clinical study in Japanese patients with psoriasis (5.3.3.2.1) and a phase II/III clinical study in Japanese patients with psoriasis (5.3.5.1.2-1) and phase I clinical studies in foreign patients with psoriasis (5.3.3.2.2, 5.3.3.2.3), a phase II clinical study in foreign patients with psoriasis (5.3.5.1.1), and phase III clinical studies in foreign patients with psoriasis (5.3.5.1.3-1 to 5.3.5.1.3-3, 5.3.5.1.4-1 to 5.3.5.1.4-3) and population pharmacokinetic analyses (5.3.3.5.1 to 5.3.3.5.2) and a study of ethnic differences (5.3.3.3.1) etc. were submitted. As the reference data, the results of an analysis of correlation between serum ustekinumab concentration and efficacy in foreign patients with psoriasis (5.3.5.3.1) etc. were submitted. Serum ustekinumab concentrations were determined by an ELISA with human IL-12 adsorbed onto the plate (lower limit of quantification, 0.08 μg/mL) or an ECLIA using monoclonal antibodies against the variable region of ustekinumab (lower limit of quantification, 16.88 ng/mL). Anti-ustekinumab antibodies were measured by an enzyme immunoassay (EIA) and neutralizing antibodies were measured by human IL-12-induced IFN-γ production by NK cells. Unless otherwise specified, the data and pharmacokinetic parameters are expressed as the mean or the mean ± SD.

4.(i).A.(1) Pharmacokinetics in patients with psoriasis

Japanese clinical studies

4.(i).A.(1).1) Single subcutaneous administration study (5.3.3.2.1, Study JNS009-JPN-01 [February 2006 to March 2007])

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A placebo-controlled, randomized, double-blind study was conducted in Japanese patients with psoriasis vulgaris (n = 24, 64.89 ± 9.90 kg). The pharmacokinetic parameters following a single subcutaneous administration of 22.5, 45, or 90 mg of ustekinumab were as shown in Table 8. The increase in C_{max} tended to be more than dose-proportional at doses up to 90 mg and was dose-proportional between doses of 22.5 mg and 45 mg. The AUC_{∞} increased in a dose-proportional manner and the $t_{1/2}$ was almost constant, regardless of dose.

Table 8. Pharmacokinetic parameters following a single subcutaneous administration of ustekinumab to Japanese patients with psoriasis vulgaris

Dose	C_{max} (μg/mL)	$AUC_{0\text{-}84day}$ (μg.day/mL)	AUC_{∞} (μg.day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL/F (mL/day)	Vz/F (L)
22.5 mg	1.412 ± 0.380	49.93 ± 11.04	70.59 ± 32.29	6.99 (4.0-27.0)	53.48 ± 79.19	364.49 ± 126.50	18.84 ± 17.04
45 mg	3.034 ± 0.636	105.30 ± 34.95	139.87 ± 80.14	10.48 (4.0-14.00)	39.07 ± 41.88	451.29 ± 195.23	18.23 ± 6.82
90 mg	8.507 ± 2.397	222.80 ± 72.67	242.97 ± 78.45	10.49 (4.0-14.00)	24.38 ± 8.30	385.15 ± 170.79	14.41 ± 11.54

Mean ± SD, Median (Min-Max) for t_{max}

4.(i).A.(1).2) Multiple subcutaneous administration study (5.3.5.1.2-1 to 5.3.5.1.2-2, Study JNS009-JPN-02 [March 2008 to March 2010])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in Japanese patients with plaque psoriasis (n = 158, 71.95 ± 14.00 kg). When 45 and 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks, at each sampling timepoint from Week 4 through Week 64, serum ustekinumab concentrations were almost dose-proportional and the trough serum concentrations of ustekinumab (median)[5] were 0.25 and 0.74 μg/mL, respectively, at Week 16, 0.25 and 0.65 μg/mL, respectively, at Week 28, 0.28 and 0.55 μg/mL, respectively, at Week 40, 0.29 and 0.67 μg/mL, respectively, at Week 52, and 0.31 and 0.76 μg/mL, respectively, at Week 64 and it was considered that the steady-state serum concentrations of ustekinumab were achieved by Week 28.

Foreign clinical studies

4.(i).A.(1).3) Single intravenous administration study (5.3.3.2.2, Study C0379T01 [April 2001 to August 2002])

An open-label, single ascending dose study was conducted in foreign patients with psoriasis vulgaris (n = 18, 92.98 ± 23.71 kg). The pharmacokinetic parameters following single ascending intravenous administrations of 0.09, 0.27, 0.9, and 4.5 mg/kg of ustekinumab were as shown in Table 9. C_{max} was reached immediately after intravenous infusion and then ustekinumab was eliminated biphasically until Week 16. The C_{max} and AUC_{∞} were dose-proportional over the dose range studied and the CL and Vd_z were constant, regardless of dose. The Vd_z was similar to the blood volume.

Table 9. Pharmacokinetic parameters following a single intravenous administration of ustekinumab to foreign patients with psoriasis vulgaris

Dose	C_{max} (μg/mL)	AUC_{∞} (μg.day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	Vd_z (mL/kg)
0.09 mg/kg	2.7 ± 0.5	48.2 ± 8.0	27.0 ± 7.5	1.90 ± 0.28	74.5 ± 24.1
0.27 mg/kg	8.9 ± 1.6	127.6 ± 14.3	18.5 ± 3.6	2.14 ± 0.26	56.1 ± 6.5
0.9 mg/kg	25.5 ± 7.2	434.7 ± 133.3	25.9 ± 3.7	2.22 ± 0.63	82.1 ± 23.6
4.5 mg/kg	136.8 ± 17.2	2346.8 ± 359.0	23.7 ± 5.7	1.96 ± 0.34	66.2 ± 15.4

Mean ± SD

[5] Data through Week 64 from subjects subcutaneously treated with ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 58-64 subjects; 90 mg group, 53-62 subjects; the placebo group was not included.)

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4.(i).A.(1).4) Single subcutaneous administration study (5.3.3.2.3, Study C0379T02 [June 2002 to May 2003])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with psoriasis vulgaris (n = 21, 96.4 ± 14.0 kg). The pharmacokinetic parameters following a single subcutaneous administration of 0.27, 0.675, 1.35, or 2.7 mg/kg of ustekinumab were as shown in Table 10. The C_{max} and AUC_{∞} increased in an almost dose-proportional manner over the dose range studied. The $t_{1/2}$ slightly increased dose-dependently though an adequate assessment was difficult for the low-dose group. The absolute bioavailability calculated from AUC_{∞} values after intravenous (Study T01) and subcutaneous (Study T02) administration was approximately 57.2%.

Table 10. Pharmacokinetic parameters following a single subcutaneous administration of ustekinumab to foreign patients with psoriasis vulgaris

Dose	C_{max} (μg/mL)	AUC_{∞} (μg.day/mL)	t_{max} (day)	$t_{1/2}$ (day)	F* (%)	CL/F (mL/day/kg)	Vz/F (mL/kg)
0.27 mg/kg	3.08 ± 1.70	90.8 ± 35.8	14.2 (7.1-15.1)	14.9 ± 4.6	67.9 ± 26.6	3.43 ± 1.65	72.8 ± 34.2
0.675 mg/kg	5.22 ± 2.58	169.7 ± 39.4	14.0 (4.0-14.3)	17.3 ± 2.5	49.3 ± 11.1	4.20 ± 0.95	106.1 ± 34.9
1.35 mg/kg	7.21 ± 2.39	323.1 ± 86.7	10.7 (7.0-14.2)	21.2 ± 3.6	47.9 ± 12.6	4.34 ± 0.95	131.1 ± 29.2
2.7 mg/kg	14.10 ± 2.82	832.3 ± 390.0	14.0 (7.1-14.1)	28.6 ± 9.3	61.4 ± 28.8	4.17 ± 2.75	144.4 ± 33.7

Mean ± SD, Median (Min-Max) for t_{max} *: Calculated as the ratio of AUC_{∞} after subcutaneous administration (Study T02) to AUC_{∞} after intravenous administration (Study T01)

4.(i).A.(1).5) Single or multiple subcutaneous administration study (5.3.5.1.1, Study C0379T04 [June 2003 to March 2005])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 320, 93.0 ± 22.7 kg). The pharmacokinetic parameters following a single subcutaneous administration or 4 weekly subcutaneous administrations of 45 or 90 mg of ustekinumab were as shown in Table 11 (Pharmacokinetic analysis population, 110 subjects). The $t_{1/2}$ following 4 weekly administrations of ustekinumab was similar to that following a single subcutaneous administration of ustekinumab.

Table 11. Pharmacokinetic parameters following a single subcutaneous administration or 4 weekly subcutaneous administrations of ustekinumab to foreign patients with psoriasis vulgaris

Dose		C_{max} (μg/mL)	AUC_{∞} (μg.day/mL)	t_{max} (day)	$t_{1/2}$ (day)
Single dose	45 mg	2.7 ± 1.2	196.7 ± 298.2	13.5 (1.9-58.2)	45.6 ± 80.2
	90 mg	6.1 ± 3.6	274.9 ± 206.5	7.0 (2.9-27.1)	26.7 ± 19.3
Multiple doses	45 mg	13.6 ± 5.7	-	3.0 (0.9-35.0)	24.9 ± 7.9
	90 mg	22.9 ± 13.1	-	3.0 (0.9-14.0)	28.1 ± 7.3

Mean ± SD, Median (Min-Max) for t_{max}

4.(i).A.(1).6) Multiple subcutaneous administration study (5.3.5.1.3-1 to 5.3.5.1.3-3, Study C0743T08 [December 2005 to ongoing (data cut-off of March 2009)])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 766, 93.88 ± 23.69 kg), to whom 45 or 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks. At each sampling timepoint from Week 4 through Week 28, serum ustekinumab concentrations were almost dose-proportional and the trough serum concentrations of ustekinumab (median)[6] in the 45 and 90 mg

[6] Data through Week 28 were obtained from subjects subcutaneously administered ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 242-253 subjects; 90 mg group, 236-253 subjects; the placebo group was not included.). Data at and after Week 52 were obtained from subjects who were re-randomized to receive dosing every 12 weeks at Week 40 (45 mg group, 52-75 subjects; 90 mg group,

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groups were 0.25 and 0.49 μg/mL, respectively, at Week 16; 0.21 and 0.47 μg/mL, respectively, at Week 28; 0.26 and 0.58 μg/mL, respectively, at Week 52; 0.50 and 0.89 μg/mL, respectively, at Week 88; 0.49 and 0.88 μg/mL, respectively, at Week 112; and 0.44 and 1.08 μg/mL, respectively, at Week 148.

4.(i).A.(1).7) Multiple subcutaneous administration study (5.3.5.1.4-1 to 5.3.5.1.4-3, Study C0743T09 [March 2006 to ongoing (data cut-off of August 2008)])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 1230, 90.99 ± 21.28 kg). When 45 or 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks, serum ustekinumab concentrations were dose-proportional and the trough serum concentrations of ustekinumab (median)[7] in the 45 and 90 mg groups were 0.37 and 0.65 μg/mL, respectively, at Week 16; 0.34 and 0.56 μg/mL, respectively, at Week 28; 0.36 and 0.64 μg/mL, respectively, at Week 40; and 0.40 and 0.68 μg/mL, respectively, at Week 52. The steady-state serum concentrations of ustekinumab were considered to be achieved by Week 28. When 45 or 90 mg of ustekinumab were subcutaneously administered every 8 weeks beginning at Week 28, the trough serum concentrations of ustekinumab (median) at Week 52 were 3.4-fold and 2.5-fold higher, respectively, than those following dosing every 12 weeks. The liquid in vial formulation (LIV formulation) was switched to the liquid in prefilled syringe formulation (PFS formulation) at Week 52 for a long-term extension period and the trough serum concentrations of ustekinumab (median)[8] after administration of 45 and 90 mg of ustekinumab every 12 weeks were similar between the two formulations, i.e. 0.38 and 0.68 μg/mL, respectively, at Week 40 and 0.40 and 0.72 μg/mL, respectively, at Week 52 for the LIV formulation and 0.42 and 0.73 μg/mL, respectively, at Week 88 for the PFS formulation.

4.(i).A.(2) Population pharmacokinetic analysis

4.(i).A.(2).1) Population pharmacokinetic (PPK) analysis using the data from clinical studies in foreign patients with psoriasis (5.3.3.5.1)

Using the serum ustekinumab concentration data from a total of 1937 subjects (9938 sampling points) in phase III studies in foreign patients with psoriasis (Studies T08 and T09), PPK analysis was performed using non-linear mixed effect modeling (NONMEM). A one-compartment model with first-order absorption was used as a base model to build up a final model. The CL/F and Vd/F values for ustekinumab estimated from the final model were 0.465 L/day and 15.7 L, respectively. Factors that could contribute to the variability in CL/F and Vd/F were identified. Body weight, diabetes comorbidity, positive immune response to ustekinumab, albumin, creatinine clearance, gender, and

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59-84 subjects). The applicant explained that at and after Week 88, higher values were obtained because the assay method was changed from ECLIA-BV to ECLIA-MSD.

[7] Data from subjects subcutaneously administered ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 243-249 subjects; 90 mg group, 279-285 subjects). Subjects in the placebo group or subjects who failed to achieve a PASI 75 response or who were adjusted to dosing every 8 weeks at Week 28 were not included.

[8] Data from subjects who achieved a PASI 75 response at Weeks 28 and 40 and continued dosing every 12 weeks and received the PFS formulation during the long-term extension period after Week 52 (45 mg group, 206-211 subjects; 90 mg group, 260-272 subjects). Note that subjects who received placebo at Weeks 0 and 4 were included.

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alkaline phosphatase were selected as statistically significant ($P < 0.005$) covariates on CL/F and body weight, race, and diabetes co-morbidity were selected as statistically significant covariates on Vd/F. Of these covariates, the inter-subject variability due to body weight, diabetes co-morbidity, or positive immune response to ustekinumab was ≥20%.

The final model-predicted CL/F and Vd/F values (0.68 L/day and 19.5 L, respectively [median]) were approximately 55% and 37% higher, respectively, in subjects weighing >100 kg compared to subjects weighing ≤100 kg (0.44 L/day and 14.2 L, respectively [median]) and the estimated steady-state trough serum concentration of ustekinumab was approximately 30% lower in subjects weighing >100 kg compared to subjects weighing ≤100 kg.

The final model-predicted CL/F and Vd/F values were approximately 28.7% and 13.2% higher, respectively, in subjects with diabetes co-morbidity compared to subjects without diabetes and the estimated trough serum ustekinumab concentration and the estimated AUC_∞ value were approximately 20% lower in subjects with diabetes compared to those without diabetes. Moreover, the trough serum ustekinumab concentration and AUC_∞ value were approximately 40% to 50% lower in subjects with diabetes weighing >100 kg compared to those without diabetes weighing ≤100 kg.

Although the incidence of anti-ustekinumab antibody positive subjects was as low as approximately 5%, the final model-predicted CL/F value was 35.5% higher in subjects positive for anti-ustekinumab antibodies compared to antibody-negative subjects (including inconclusive subjects).

The final model-predicted CL/F value was 5.9% higher in women compared to men and the Vd/F value was 11.1% higher in non-white subjects compared to white subjects. It was considered that the effects of the renal function (creatinine clearance) and hepatic function (albumin and alkaline phosphatase) on the pharmacokinetics of ustekinumab are also small, though assessed in a limited fashion. The potential impact of 28 concomitant medications most frequently used by subjects on the CL/F of ustekinumab were evaluated in the PPK analysis and none of the concomitant medications had a significant effect.

4.(i).A.(3) Comparison of pharmacokinetics of ustekinumab between Japanese and foreign patients (5.3.3.3.1, 5.3.3.5.2)

Using the data from Japanese Study JPN-01 and Foreign Study T04, the pharmacokinetics of a single subcutaneous dose of ustekinumab were compared. The median C_{max} and AUC_∞ were 1.07- to 1.81-fold higher in Japanese patients with psoriasis compared to foreign patients and as body weight of foreign patients with psoriasis (median body weight, 89.0 kg) was 1.34-fold heavier than body weight of Japanese patients with psoriasis (median body weight, 66.20 kg), it was discussed that the pharmacokinetic differences between Japanese and foreign patients were potentially due to the effect of body weight. Using the data from Japanese Study JPN-02 and Foreign Studies T08 and T09, the pharmacokinetics of multiple subcutaneous doses of ustekinumab were also compared. The trough

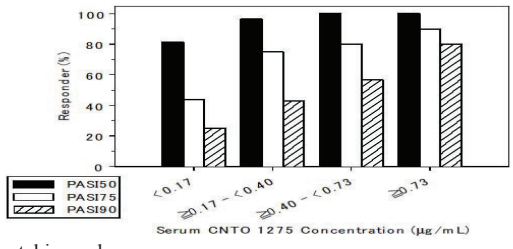
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serum concentrations of ustekinumab (median) at Week 28 were 0.25 μg/mL in the 45 mg group and 0.65 μg/mL in the 90 mg group in Japanese patients, which were 0.96- to 1.19-fold and 1.33- to 1.38-fold higher, respectively, than those in foreign patients (0.21-0.26 and 0.47-0.49 μg/mL, respectively). Based on comparison of serum ustekinumab concentrations among subjects stratified by body weight (≤70 kg or >70 kg; ≤100 kg or >100 kg), it was discussed that these differences were also due to differences in body weight.

Furthermore, as covariates in the final model obtained from the PPK analysis of phase III studies in foreign patients with psoriasis (Studies T08 and T09), the subject background data from Japanese Study JPN-02 were used to predict the serum ustekinumab concentration over time in Japanese patients with psoriasis. As a result, although the observed concentrations at Weeks 2 and 20 fell outside of the 5-to-95 percentile range of the predicted values, it was explained that the pharmacokinetic differences between Japanese and foreign patients were due to the confounding effect of body weight, as the predicted values almost agreed with the observed values.

4.(i).A.(4) Correlation between serum ustekinumab concentration and efficacy in psoriasis patients (5.3.5.1.2-1, 5.3.5.3.1)

In Japanese Study JPN-02, the proportions of subjects who achieved Psoriasis Area and Severity Index[9] (PASI) 50, 75, and 90 responses (PASI 50, PASI 75, and PASI 90 response rates, respectively) at Week 28 by serum ustekinumab (trough) concentrations following multiple subcutaneous administrations of 45 mg or 90 mg of ustekinumab were as shown in Figure 1. The PASI 75 and PASI 90 response rates increased with increasing serum ustekinumab concentrations. Foreign Studies T08 and T09 also showed a similar trend. According to subgroup analyses of responders, partial responders and nonresponders (subjects who achieved a ≥75%, ≥50% and <75%, and <50% improvement in PASI score from baseline, respectively) at Week 28 in each of Studies JPN-02, T08, and T09, the serum ustekinumab (trough) concentration (median) was higher in this order.



Serum ustekinumab concentration (μg/mL)	<0.17	≥0.17 - <0.40	≥0.40 - <0.73	≥0.73
n	32	28	30	30

Figure 1. PASI 50, 75, and 90 response rates by serum ustekinumab concentrations; Week 28 (Study JPN-02)

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Racial differences in pharmacokinetic (PK)/pharmacodynamic (PD) profile

It was explained that higher serum ustekinumab concentrations in Japanese patients compared to foreign patients were due to lower body weight of Japanese patients compared to foreign patients.

[9] The body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for erythema, infiltration/induration, and scaling, which are each rated on a 5-point scale and for area of involvement. For each of the four body areas, the three symptom scores are added and then multiplied by the area score. Each body region's score is then multiplied by the proportions to reflect its contribution to total body area (10% for head, 20% for upper extremities, 30% for trunk, 40% for lower extremities). The scores for all four body areas are added to yield the overall PASI score (Scores range from 0 to 72.0).

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Meanwhile, the trough concentration was higher, but the PASI 75 response rate tended to be lower in Japanese patients compared to foreign patients. PMDA asked the applicant to discuss racial differences in the pharmacokinetic (PK)/pharmacodynamic (PD) profile of ustekinumab.

The applicant explained as follows:
Since BSA involvement and PASI score at baseline were higher in Japanese patients with psoriasis (Study JPN-02) compared to foreign patients with psoriasis (Studies T08 and T09), the applicant considered that the severity of psoriasis at baseline may affect the pharmacokinetics and efficacy of ustekinumab. Thus, baseline PASI, Physician's Global Assessment (PGA), and Dermatology Life Quality Index scores related to severity and disease duration (years) were evaluated as potential covariates in the PPK and PPK/PD analyses of the data from Studies T08 and T09. As a result, none of them were statistically significant covariates. Also when the effects of the severity of psoriasis at baseline and disease duration (years) on the PASI response rate were evaluated by subgroup analyses of Studies JPN-02 and T08 and T09, there was no clear correlation between these factors and efficacy and moreover, no effects of other patient background factors on efficacy were suggested.

PMDA concluded that although the cause for differences in the PK/PD profile between Japanese and foreign patients is not clear, ustekinumab is generally highly effective in treating skin symptoms and these differences are not clinically relevant.

4.(i).B.(2) Pharmacokinetics and clinical response in patients with diabetes co-morbidity
Foreign Studies T08 and T09 showed a trend toward lower trough concentrations and reduced efficacy in patients with diabetes compared to those without diabetes and body weight and diabetes co-morbidity were selected as covariates on CL/F and Vd/F in the PPK analysis. PMDA asked the applicant to discuss its cause and explain whether dose adjustment is required for patients with diabetes co-morbidity.

The applicant explained as follows:
The trough serum concentration of ustekinumab estimated from the final model obtained in the PPK analysis of Studies T08 and T09 was approximately 20% lower in subjects with diabetes compared to subjects without diabetes of the same body weight and according to the pooled data from Studies T08 and T09, the PASI 75 response rate was slightly lower in subjects with diabetes than in subjects without diabetes in both subgroups of subjects weighing ≤100 kg or >100 kg. Thus, it is considered that lower serum ustekinumab concentrations and reduced efficacy in patients with diabetes are due to the effects of not only body weight but also diabetes itself, which may be attributable to altered vascular permeability and lymph distribution of drugs in patients with diabetes. On the other hand, in order to determine the effect of the severity of diabetes, the relationship between baseline HbA1c and trough serum concentration of ustekinumab/percent improvement in PASI score in Studies T08 and T09 was examined. As a result, there was a statistically significant but weak negative correlation between baseline HbA1c and both trough serum concentration of ustekinumab and percent

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improvement in PASI score. Thus, no specific dose adjustment is required for patients with diabetes co-morbidity.

PMDA accepts the above response at present, but considers that as the number of subjects with high HbA1c was limited in the clinical studies, the efficacy of ustekinumab in patients with diabetes co-morbidity needs to be further investigated, including the effect of the severity of diabetes, via post-marketing surveillance.

4.(i).B.(3) Anti-ustekinumab antibodies

The applicant explained the incidence of anti-ustekinumab antibody production and its relationship with the pharmacokinetics and efficacy of ustekinumab, etc. as follows:

The incidences of anti-ustekinumab antibody positive subjects in Japanese Study JPN-02 and Foreign Studies T04, T08, and T09 were 6.5% (10 of 153 subjects) [through Week 72], 4.1% (12 of 293 subjects) [through Week 52], 5.1% (38 of 746 subjects) [through Week 76], and 5.3% (64 of 1202 subjects) [through Week 88], respectively, and no differences between Japanese and foreign patients with psoriasis were observed. Japanese Study JPN-02 showed that the incidence of anti-ustekinumab antibody positive subjects tended to be higher in the 45 mg group (9.4%, 6 of 64 subjects) than in the 90 mg group (3.3%, 2 of 61 subjects) and a similar trend was observed also in foreign patients with psoriasis. When stratified by body weight, the incidence of anti-ustekinumab antibody positive subjects was lower in subjects weighing ≤100 kg (3.6%, 48 of 1341 subjects) than in subjects weighing >100 kg (9.1%, 55 of 606 subjects) in Studies T08 and T09. Anti-ustekinumab antibodies were detected by around Week 28 in Study JPN-02 and by around Week 52 in Studies T08 and T09 and 4.4% (13 of 297 subjects) of subjects who were retreated with ustekinumab after withdrawal from ustekinumab therapy developed anti-ustekinumab antibodies, which was similar to the incidence in the overall study population.

In Studies T02, T04, and T08, samples from 50 of 51 subjects positive for anti-ustekinumab antibodies were assessed for ustekinumab neutralizing potential and 29 (58.0%) of the 50 subjects were positive for neutralizing antibodies that are able to neutralize the pharmacological activity of ustekinumab. Some of the anti-ustekinumab antibody positive subjects were not positive for neutralizing antibodies. They had low antibody titers and probably, the neutralizing effect of antibodies could not be detected.

Following multiple subcutaneous administrations of ustekinumab to Japanese and foreign patients with psoriasis, anti-ustekinumab antibody positive subjects tended to have lower serum ustekinumab concentrations (median) than antibody negative subjects.

The PASI 75 and PASI 90 response rates at Week 28 tended to be lower in anti-ustekinumab antibody positive subjects compared to antibody negative subjects in Japanese Study JPN-02 and a similar trend was observed also in foreign studies. However, since many antibody-positive subjects achieved a

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PASI 50 response and some achieved a PASI 75 response, it was discussed that anti-ustekinumab antibody development has no significant impact on clinical response.

PMDA considers as follows:
Based on the above, no clinically relevant problems with anti-ustekinumab antibody development have been suggested at present. Meanwhile, the relationship between neutralizing activity of antibodies and the efficacy and pharmacokinetics of ustekinumab has not adequately been examined and the proportion of antibody positive subjects who were positive for neutralizing antibodies tended to be relatively high (≥50%). Taking account of these points, a further investigation on antibodies and their neutralizing activity etc. in patients with markedly reduced efficacy during continued treatment is necessary.

4.(ii) Summary of clinical efficacy and safety

4.(ii).A Summary of the submitted data

As the efficacy and safety evaluation data, the results from a phase I study (Study JNS009-JPN-01 [5.3.3.2.1]) and a phase II/III study (Study JNS009-JPN-02 [5.3.5.1.2-1 to 5.3.5.1.2-2]) in Japanese patients with psoriasis and a phase I single intravenous administration study (Study C0379T01 [5.3.3.2.2]), a phase I single subcutaneous administration study (Study C0379T02 [5.3.3.2.3]), a phase II study (Study C0379T04 [5.3.5.1.1]), a phase II study (Study C0743T10 [5.3.5.4.1]), a phase III study (Study C0743T08 [5.3.5.1.3-1 to 5.3.5.1.3-3]), and a phase III study (Study C0743T09 [5.3.5.1.4-1 to 5.3.5.1.4-3]) in foreign patients with psoriasis were submitted.

4.(ii).A.(1) Studies in Japanese patients

4.(ii).A.(1).1) Phase I study (5.3.3.2.1, JNS009-JPN-01 [February 2006 to March 2007])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in patients with psoriasis vulgaris (Target sample size of 24 subjects [6 subjects each in the ustekinumab 22.5 mg, 45 mg, and 90 mg and placebo groups]) to evaluate the efficacy, safety, and pharmacokinetics of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

A single subcutaneous dose of 22.5 mg of ustekinumab (6 subjects) or placebo (2 subjects) was to be administered in STEP1, a single subcutaneous dose of 45 mg of ustekinumab (6 subjects) or placebo (2 subjects) in STEP2, and a single subcutaneous dose of 90 mg of ustekinumab (6 subjects) or placebo (2 subjects) in STEP3. After safety was confirmed in each STEP, the study was to move to the next STEP. Subjects were followed through Week 24.

All of the 24 subjects treated were included in the Full Analysis Set (FAS), which was used as the safety population, and 23 subjects (6 subjects in the 22.5 mg group, 6 subjects in the 45 mg group, 6 subjects in the 90 mg group, 5 subjects in the placebo group), excluding 1 subject in the placebo group

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who received rescue medication due to exacerbation of the primary disease, were included in the Per Protocol Set, which was used as the primary efficacy population.

The Psoriasis Area and Severity Index[10] (PASI) 75 response rate[11] at Week 12 was an efficacy endpoint. The PASI 75 response rates at Week 12 were 33.3% (2 of 6 subjects) in the 22.5 mg group, 100% (6 of 6 subjects) in the 45 mg group, 75% (3 of 4 subjects) in the 90 mg group, and 0% in the placebo group, and the ustekinumab groups showed greater improvement compared to the placebo group.

Adverse events (including abnormal laboratory test values) occurred in all subjects (24 of 24 subjects). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Adverse drug reactions[12] occurred in all subjects (24 of 24 subjects) and those reported by ≥2 subjects in any of the ustekinumab groups were nasopharyngitis [33.3% (2 of 6 subjects) in the 22.5 mg group, 16.7% (1 of 6 subjects) in the 45 mg group, 33.3% (2 of 6 subjects) in the 90 mg group, 0% (0 of 6 subjects) in the placebo group], activated partial thromboplastin time prolonged [50.0% (3 of 6 subjects) in the 22.5 mg group, 33.3% (2 of 6 subjects) in the 45 mg group, 33.3% (2 of 6 subjects) in the 90 mg group, 0% (0 of 6 subjects) in the placebo group], and B-lymphocyte count decreased [33.3% (2 of 6 subjects) in the 22.5 mg group, 50.0% (3 of 6 subjects) in the 45 mg group, 16.7% (1 of 6 subjects) in the 90 mg group, 66.7% (4 of 6 subjects) in the placebo group].

4.(ii).A.(1).2) Phase II/III study (5.3.5.1.2-1 to 5.3.5.1.2-2, JNS009-JPN-02 [March 2008 to March 2010])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in Japanese patients with moderate to severe[13] plaque psoriasis (psoriasis vulgaris, psoriatic arthritis) (Target sample size of 150 [60 subjects per active treatment group, 30 subjects in the placebo group]) to evaluate the efficacy and safety of ustekinumab.

Ustekinumab 45 or 90 mg or placebo was to be subcutaneously administered according to Table 12. Subjects were followed for efficacy and safety through Week 64 and Week 72, respectively.

When the pharmacokinetics of ustekinumab were compared between Japanese Study JPN-01 and Foreign Study T04, the pharmacokinetics of ustekinumab were considered similar between Japanese

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[10] The body is divided into 4 regions: the head, upper extremities, trunk, and lower extremities. Each of these areas is assessed separately for erythema, infiltration/induration, and scaling, which are each rated on a 5-point scale and for area of involvement. For each of the four body areas, the three symptom scores are added and then multiplied by the area score. Each body region's score is then multiplied by the proportions to reflect its contribution to total body area (10% for head, 20% for upper extremities, 30% for trunk, 40% for lower extremities). The scores for all four body areas are added to yield the overall PASI score (Scores range from 0 to 72.0).

[11] The proportion of subjects who achieved a ≥75% reduction in PASI score from baseline.

[12] Adverse events for which a causal relationship to study drug could not be denied (adverse events other than those assessed as "unrelated to" study drug).

[13] Body surface area (BSA) involvement of ≥10% and PASI score of ≥12.

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and foreign patients of the same body weight range [see "4.(i) Summary of clinical pharmacology studies"] and 9 of 10 patients who received 45 or 90 mg of ustekinumab achieved a PASI 75 response in Study JPN-01. Thus, for this study, the same dosing regimen as that for foreign phase III studies (Studies T08 and T09) was selected.

Table 12. Ustekinumab dosing schedule for each treatment group

	Week 0	Week 4	Week 12	Week 16	Every 12 weeks after Week 28 through Week 52
45 mg group	45 mg	45 mg	Placebo	45 mg	45 mg
90 mg group	90 mg	90 mg	Placebo	90 mg	90 mg
Placebo→45 mg group	Placebo	Placebo	45 mg	45 mg	45 mg
Placebo→90 mg group	Placebo	Placebo	90 mg	90 mg	90 mg

All of the 158 subjects treated (64 subjects in the 45 mg group, 62 subjects in the 90 mg group, 32 subjects in the placebo group) were included in the safety population and 157 subjects (64 subjects in the 45 mg group, 62 subjects in the 90 mg group, 15 subjects in the placebo→45 mg group, 16 subjects in the placebo→90 mg group), excluding 1 subject for whom an emergency code break was required before efficacy data collection, were included in the FAS, which was used as the primary efficacy population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 was 59.4% (38 of 64 subjects) in the 45 mg group, 67.7% (42 of 62 subjects) in the 90 mg group, and 6.5% (2 of 31 subjects) in the placebo group, as shown in Table 13, and the differences between both of the ustekinumab groups and the placebo group were statistically significant ($P < 0.0001$ for both [Fisher's exact test], using Holm's method). The secondary endpoints of the PASI 50 response rate and the PASI 90 response rate were as shown in Table 13.

Table 13. PASI response rate at Week 12

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
PASI 50 response rate	12.9 (4/31)	82.8 (53/64)	83.9 (52/62)
PASI 75 response rate	6.5 (2/31)	59.4 (38/64)	67.7 (42/62)
PASI 90 response rate	3.2 (1/31)	32.8 (21/64)	43.5 (27/62)

% (n)

Of the 157 patients, 22 patients had joint symptoms and among these patients, the PASI 75 response rates at Week 12 were 83.3% (5 of 6 subjects) in the 45 mg group, 46.2% (6 of 13 subjects) in the 90 mg group, and 0% (0 of 3 subjects) in the placebo group.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 65.6% (42 of 64 subjects) (85 events) in the 45 mg group, 59.7% (37 of 62 subjects) (80 events) in the 90 mg group, and 65.6% (21 of 32 subjects) (38 events) in the placebo group. No deaths were reported. The incidences of serious adverse events were 4.8% (3 of 62 subjects) (4 events) (pneumonia; prostate cancer; and psoriasis and osteonecrosis, 1 subject each) in the 90 mg group and 6.3% (2 of 32 subjects) (3 events) (cardiac failure congestive [1 subject], psoriasis and dermatitis exfoliative [1 subject]) in the placebo group, and although a causal relationship to study drug could not

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be denied for pneumonia, prostate cancer, and psoriasis in the 90 mg group and cardiac failure congestive in the placebo group, the outcomes of all events were reported as resolved or improved. The incidences of adverse events leading to treatment discontinuation were 6.5% (4 of 62 subjects) (4 events) (psoriasis [2 subjects], pneumonia [1 subject], prostate cancer [1 subject]) in the 90 mg group and 6.3% (2 of 32 subjects) (3 events) (psoriasis [1 subject], psoriasis and dermatitis exfoliative [1 subject]) in the placebo group, and a causal relationship to study drug could not be denied for pneumonia, prostate cancer, and psoriasis (2 subjects) in the 90 mg group and the outcomes of all events were reported as resolved or improved.

The incidences of adverse drug reactions were 54.7% (35 of 64 subjects) (59 events) in the 45 mg group, 45.2% (28 of 62 subjects) (53 events) in the 90 mg group, and 59.4% (19 of 32 subjects) (30 events) in the placebo group and those reported by ≥2 subjects in any group were as shown in Table 14.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 72[14] were 96.9% (62 of 64 subjects) (447 events) in the 45 mg group, 98.4% (61 of 62 subjects) (417 events) in the 90 mg group, 93.3% (14 of 15 subjects) (89 events) in the placebo→45 mg group, and 100% (13 of 13 subjects) (69 events) in the placebo→90 mg group. No deaths were reported. The incidences of serious adverse events were 7.8% (5 of 64 subjects) (7 events) in the 45 mg group, 9.7% (6 of 62 subjects) (9 events) in the 90 mg group, 6.7% (1 of 15 subjects) (1 event) in the placebo→45 mg group, and 7.7% (1 of 13 subjects) (1 event) in the placebo→90 mg group. Those occurring after Week 12 were as follows: 45 mg group (fall; cellulitis; cervix carcinoma stage 0; cataract; and pharyngitis, colonic polyp, and diabetes mellitus, 1 subject each), 90 mg group (dislocation of the prosthetic femoral head; fall; cerebral haemorrhage; and cataract, 1 subject each), placebo→45 mg group (lumbar spinal stenosis [1 subject]), and placebo→90 mg group (electrocardiogram abnormal [1 subject]). Although a causal relationship to study drug could not be denied for pharyngitis, colonic polyp, and cellulitis in the 45 mg group, cerebral haemorrhage and cataract in the 90 mg group, and lumbar spinal stenosis in the placebo→45 mg group, the outcomes of all events were reported as resolved or improved, except that the outcome of cerebral haemorrhage (1 subject in the 90 mg group) was reported as improved with sequelae.

The incidences of adverse events leading to treatment discontinuation after Week 12 were 1.6% (1 of 64 subjects) (1 event) (cervix carcinoma stage 0) in the 45 mg group, 1.6% (1 of 62 subjects) (1 event) (cerebral haemorrhage) in the 90 mg group, and 7.7% (1 of 13 subjects) (1 event) (hepatic steatosis) in the placebo→90 mg group. Although the 1 subject discontinued treatment due to hepatic steatosis after Week 12, hepatic steatosis occurred during the placebo administration period before Week 12.

[14] From Week 12 through Week 72, after crossover to ustekinumab.

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The incidences of adverse drug reactions were 87.5% (56 of 64 subjects) (304 events) in the 45 mg group, 87.1% (54 of 62 subjects) (300 events) in the 90 mg group, 93.3% (14 of 15 subjects) (74 events) in the placebo→45 mg group, and 92.3% (12 of 13 subjects) (42 events) in the placebo→90 mg group. Adverse drug reactions reported by ≥2 subjects in any group were as shown in Table 15.

Table 14. Adverse drug reactions reported by ≥2 subjects in any group (through Week 12)

Preferred terms	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
Nasopharyngitis	2 (6.3)	9 (14.1)	8 (12.9)
Folliculitis	0	1 (1.6)	2 (3.2)
Psoriasis	5 (15.6)	1 (1.6)	3 (4.8)
Eczema	0	1 (1.6)	2 (3.2)
Arthralgia	0	3 (4.7)	0
Blood triglycerides increased	1 (3.1)	4 (6.3)	0
Eosinophil count increased	1 (3.1)	2 (3.1)	3 (4.8)
Basophil count increased	0	2 (3.1)	2 (3.2)
Blood uric acid increased	0	1 (1.6)	2 (3.2)
Lymphocyte count decreased	0	2 (3.1)	0

n (%)

Table 15. Adverse drug reactions reported by ≥2 subjects in any group (through Week 72)

Preferred terms	Placebo→45 mg	Placebo→90 mg	45 mg	90 mg
Nasopharyngitis	7 (46.7)	7 (53.8)	27 (42.2)	26 (41.9)
Influenza	0	0	2 (3.1)	5 (8.1)
Folliculitis	2 (13.3)	0	2 (3.1)	4 (6.5)
Cystitis	0	0	2 (3.1)	0
Skin papilloma	0	0	0	3 (4.8)
Seasonal allergy	1 (6.7)	0	2 (3.1)	5 (8.1)
Hyperlipidaemia	1 (6.7)	0	3 (4.7)	0
Headache	0	1 (7.7)	5 (7.8)	1 (1.6)
Conjunctivitis	0	0	2 (3.1)	1 (1.6)
Ventricular extrasystoles	0	0	2 (3.1)	2 (3.2)
Hypertension	0	0	2 (3.1)	4 (6.5)
Rhinitis allergic	1 (6.7)	0	1 (1.6)	4 (6.5)
Oropharyngeal pain	0	1 (7.7)	0	2 (3.2)
Dental caries	0	0	3 (4.7)	3 (4.8)
Diarrhoea	0	1 (7.7)	4 (6.3)	0
Periodontal disease	1 (6.7)	0	0	2 (3.2)
Enterocolitis	0	0	2 (3.1)	0
Hepatic function abnormal	0	0	3 (4.7)	3 (4.8)
Eczema	1 (6.7)	0	2 (3.1)	3 (4.8)
Psoriasis	0	0	3 (4.7)	4 (6.5)
Urticaria	1 (6.7)	1 (7.7)	1 (1.6)	2 (3.2)
Acne	0	1 (7.7)	0	3 (4.8)
Xeroderma	1 (6.7)	0	2 (3.1)	2 (3.2)
Heat rash	0	0	2 (3.1)	0
Pruritus	0	0	2 (3.1)	0
Back pain	1 (6.7)	0	1 (1.6)	2 (3.2)
Arthralgia	0	1 (7.7)	6 (9.4)	1 (1.6)
Pain in extremity	0	0	2 (3.1)	0
Pyrexia	1 (6.7)	1 (7.7)	2 (3.1)	0
Blood triglycerides increased	2 (13.3)	1 (7.7)	10 (15.6)	8 (12.9)
Blood creatine phosphokinase increased	2 (13.3)	2 (15.4)	7 (10.9)	9 (14.5)
Alanine aminotransferase increased	2 (13.3)	2 (15.4)	4 (6.3)	6 (9.7)
Eosinophil count increased	0	0	4 (6.3)	6 (9.7)
White blood cell count increased	0	1 (7.7)	4 (6.3)	4 (6.5)
Blood lactate dehydrogenase increased	1 (6.7)	0	5 (7.8)	3 (4.8)
Lymphocyte count decreased	1 (6.7)	0	5 (7.8)	1 (1.6)
Basophil count increased	0	0	3 (4.7)	4 (6.5)
Glucose urine present	1 (6.7)	0	2 (3.1)	3 (4.8)
Blood cholesterol increased	1 (6.7)	0	3 (4.7)	0
Blood amylase increased	0	1 (7.7)	1 (1.6)	2 (3.2)
Blood bilirubin increased	0	1 (7.7)	2 (3.1)	1 (1.6)
C-reactive protein increased	1 (6.7)	0	1 (1.6)	3 (4.8)

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Protein urine present	0	0	0	3 (4.8)
Blood creatinine increased	0	0	0	2 (3.2)
Blood uric acid increased	0	0	1 (1.6)	2 (3.2)
Liver function test abnormal	0	0	0	3 (4.8)
Red blood cell count increased	1 (6.7)	0	0	2 (3.2)
White blood cell count decreased	0	0	2 (3.1)	1 (1.6)
Blood phosphorus decreased	1 (6.7)	0	0	2 (3.2)
Blood phosphorus increased	0	0	2 (3.1)	0
Blood urea increased	0	0	0	2 (3.2)
Blood urine present	0	0	0	2 (3.2)
Weight increased	0	0	2 (3.1)	0

n(%)

Based on the above, the applicant explained as follows:

The efficacy of ustekinumab was confirmed. When the efficacy of ustekinumab at different dose levels was examined, the PASI 75 response rate at Week 12 was 8.3% higher in the 90 mg group compared to the 45 mg group while the PASI 50 response rate was almost the same in the 45 mg and 90 mg groups, which indicated that both dose levels of ustekinumab can achieve clinically significant improvement in skin lesions in most patients, etc. Thus, the recommended clinical dose of ustekinumab should be 45 mg. On the other hand, given that foreign studies showed that the trough serum concentration of ustekinumab and the PASI 75 response rate in the 90 mg group tended to be lower in subjects weighing >100 kg compared to those weighing ≤100 kg, etc., it was decided that a 90 mg dose may be used in patients weighing >100 kg.

4.(ii).A.(2) Studies in foreign patients

4.(ii).A.(2).1) Single intravenous administration study (5.3.3.2.2, C0379T01 [April 2001 to August 2002])

An open-label, uncontrolled study was conducted in patients with moderate to severe psoriasis vulgaris (Target sample size of 23 [4 subjects each in the 0.09 and 0.27 mg/kg groups, 5 subjects each in the 0.9, 4.5, and 18 mg/kg groups]) to evaluate the pharmacokinetics, efficacy, and safety of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

A single dose of 0.09, 0.27, 0.90, 4.5, or 18 mg/kg[15] of ustekinumab was to be administered as an intravenous infusion over ≥2 hours. Ustekinumab treatment was started with the lowest dose and after safety was confirmed, the dose was to be escalated to the next dose level. Subjects were followed through Week 16.

All of the 18 subjects treated[16] (4 subjects each in the 0.09 and 0.27 mg/kg groups, 5 subjects each in the 0.9 and 4.5 mg/kg groups) were included in the safety and efficacy populations.

The percent improvement in PASI score from baseline (mean ± SD) was an efficacy endpoint. The percent improvements in the 0.09, 0.27, 0.9, and 4.5 mg/kg groups were 68.5 ± 25.1%, 54.3 ± 49.1%,

[15] Although the study was intended to be conducted at doses of 0.1, 0.3, 1.0, 5.0, and 20 mg/kg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

[16] An 18 mg/kg group was not included in the study due to protocol amendments.

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73.6 ± 20.0%, and 97.1 ± 4.9%, respectively, at Week 12, and 58.1 ± 32.5%, 50.0 ± 45.0%, 80.4 ± 18.9%, and 94.9 ± 7.2%, respectively, at Week 16.

Adverse events (including abnormal laboratory test values) occurred in all subjects (18 of 18 subjects). No deaths were reported. A serious adverse event occurred in 1 subject in the 4.5 mg/kg group (herniated disk) and its causal relationship to study drug was denied. There were no adverse events leading to treatment discontinuation.

Adverse drug reactions occurred in all subjects except for 2 subjects in the 0.9 mg/kg group and 1 subject in the 4.5 mg/kg group. Those reported by ≥2 subjects in any group were lymphocyte count decreased (3 subjects in the 0.09 mg/kg group, 3 subjects in the 0.27 mg/kg group, 2 subjects in the 0.9 mg/kg group, 2 subjects in the 4.5 mg/kg group) and headache (1 subject in the 0.09 mg/kg group, 3 subjects in the 0.27 mg/kg group, 1 subject in the 0.9 mg/kg group, 1 subject in the 4.5 mg/kg group).

4.(ii).A.(2).2) Single subcutaneous administration study (5.3.3.2.3, C0379T02 [June 2002 to May 2003])

A placebo-controlled, double-blind, parallel-group, comparative study was conducted in patients with moderate to severe psoriasis vulgaris (Target sample size of 20 [4 subjects each in the ustekinumab 0.27, 0.675, 1.35, and 2.7 mg/kg and placebo groups]) to evaluate the pharmacokinetics, efficacy, and safety of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

In Cohort 1, a single subcutaneous dose of 0.27 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 2, a single subcutaneous dose of 0.675 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 3, a single subcutaneous dose of 1.35 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 4, a single subcutaneous dose of 2.7 mg/kg of ustekinumab (4 subjects) or placebo (1 subject)[17] was to be administered. After safety was confirmed in each cohort, the next dose cohort was to be initiated. Subjects were followed through Week 24.

All of the 21 subjects treated (5 subjects in the 0.27 mg/kg group, 4 subjects each in the 0.675, 1.35, and 2.7 mg/kg and placebo groups) were included in the safety and efficacy populations.

The percent improvement in PASI score from baseline (mean ± SD) was an efficacy endpoint. The percent improvements in the 0.27, 0.675, 1.35, 2.7 mg/kg, and placebo groups were 53.1 ± 26.0%, 76.7 ± 13.3%, 57.3 ± 11.3%, 85.4 ± 8.0%, and 43.4 ± 27.4%, respectively, at Week 12 and 25.1 ± 32.8%, 33.2 ± 45.1%, 44.9 ± 27.5%, 76.5 ± 10.2%, and -5.0 ± 52.6%, respectively, at Week 24.

[17] Although the study was intended to be conducted at doses of 0.3, 0.75, 1.5, and 3.0 mg/kg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

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The incidences of adverse events (including abnormal laboratory test values) were 100% (5 of 5 subjects) in the 0.27 mg/kg group, 75% (3 of 4 subjects) in the 0.675 mg/kg group, 75% (3 of 4 subjects) in the 1.35 mg/kg group, 100% (4 of 4 subjects) in the 2.7 mg/kg group, and 100% (4 of 4 subjects) in the placebo group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

The incidences of adverse drug reactions were 100% (5 of 5 subjects) in the 0.27 mg/kg group, 75% (3 of 4 subjects) in the 0.675 mg/kg group, 50% (2 of 4 subjects) in the 1.35 mg/kg group, 100% (4 of 4 subjects) in the 2.7 mg/kg group, and 75% (3 of 4 subjects) in the placebo group, and those reported by ≥2 subjects in any group were blood creatine phosphokinase increased (3 subjects in the 0.27 mg group, 1 subject in the 0.675 mg/kg group, 0 subjects in the 1.35 mg/kg group, 1 subject in the 2.7 mg/kg group, 1 subject in the placebo group).

4.(ii).A.(2).3) Phase II study (5.3.5.1.1, C0379T04 [June 2003 to March 2005])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 300 [60 subjects per group]) to evaluate the efficacy and safety of ustekinumab.

According to Table 16, 45 or 90 mg[18] of ustekinumab or placebo was to be administered subcutaneously. Subjects were followed for safety and efficacy through Week 32 and Week 36, respectively.

In Study T01, 2 of 4 subjects in the 0.27 mg/kg group achieved a PASI 75 response and the bioavailability of ustekinumab following subcutaneous administration was approximately 62.5% and the mean body weight of psoriasis patients was approximately 95 kg. Taking account of these findings, an ustekinumab subcutaneous fixed dose of 45 mg was selected as the lowest dose for this study. Since subjects with AUC_{∞} >450 μg·day/mL or C_{max} >27 μg/mL achieved a PASI 75 response in Studies T01 and T02, a compartment model analysis was performed using the data from the two studies and 90 mg (single dose), 180 mg (45 mg/week × 4), and 360 mg (90 mg/week × 4) as well as 45 mg (single dose) were selected to span the above-mentioned levels of AUC_{∞} and C_{max}.

Table 16. Ustekinumab dosing schedule for each treatment group

	Week 0	Weeks 1, 2, 3	Week 16	Week 20
45 mg single-dose group	Ustekinumab 45 mg	Placebo	Ustekinumab 45 mg or placebo[a]	Placebo
90 mg single-dose group	Ustekinumab 90 mg	Placebo	Ustekinumab 90 mg or placebo[a]	Placebo
45 mg multiple-dose group	Ustekinumab 45 mg	Ustekinumab 45 mg	Ustekinumab 45 mg or placebo[a]	Placebo
90 mg multiple-dose group	Ustekinumab 90 mg	Ustekinumab 90 mg	Ustekinumab 90 mg or placebo[a]	Placebo
Placebo group	Placebo	Placebo	Placebo	Ustekinumab 90 mg

a: Subjects with relative PGA ≥3 were to receive ustekinumab and subjects with relative PGA <3 were to receive placebo.

[18] Although the study was intended to be conducted at doses of 50 and 100 mg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

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The efficacy population included 320 randomized subjects (64 subjects per group). Excluding 2 subjects who did not receive study drug (1 subject each in the 45 mg single-dose and 90 mg single-dose groups) and including 1 subject who mistakenly received placebo before randomization, 319 subjects were included in the safety population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 was 51.6% (33 of 64 subjects) in the 45 mg single-dose group, 59.4% (38 of 64 subjects) in the 90 mg single-dose group, 67.2% (43 of 64 subjects) in the 45 mg multiple-dose group, 81.3% (52 of 64 subjects) in the 90 mg multiple-dose group, and 1.6% (1 of 64 subjects) in the placebo group and subjects treated with ustekinumab showed significantly greater improvement compared with subjects treated with placebo ($P < 0.001$, pairwise comparisons using the Chochran-Mantel-Haenzel χ^2 test).

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 36 were 95.2% (60 of 63 subjects) in the 45 mg single-dose group, 87.5% (56 of 64 subjects) in the 90 mg single-dose group, 87.3% (55 of 63 subjects) in the 45 mg multiple-dose group, 72.6% (45 of 62 subjects) in the 90 mg multiple-dose group, 51.0% (25 of 49 subjects) in the placebo→90 mg (after Week 20) group, and 71.6% (48 of 67 subjects) in the placebo group (through Week 20). No deaths were reported. The incidences of serious adverse events were 4.8% (3 of 63 subjects) (acute psychosis; cellulitis; and rib fracture, 1 subject each) in the 45 mg single-dose group, 4.7% (3 of 64 subjects) (myocardial infarction; abdominal hernia; and coronary artery disease, 1 subject each) in the 90 mg single-dose group, 3.2% (2 of 63 subjects) (cerebrovascular accident; and chest pain, 1 subject each) in the 45 mg multiple-dose group, 8.1% (5 of 62 subjects) (urinary tract infection; acute myocardial infarction and viral infection; uterine leiomyoma; pneumonia and cardiac failure congestive; and acute psychosis and polysubstance dependence, 1 subject each) in the 90 mg multiple-dose group, 2.0% (1 of 49 subjects) (hepatic enzyme increased) in the placebo→90 mg (after Week 20) group, and 1.5% (1 of 67 subjects) (psoriasis) in the placebo group and a causal relationship to study drug could not be denied for cellulitis, myocardial infarction, coronary artery disease, cerebrovascular accident, urinary tract infection, acute myocardial infarction, viral infection, pneumonia, cardiac failure congestive, and hepatic enzyme increased. The outcomes of coronary artery disease, cardiac failure congestive, acute psychosis, and polysubstance dependence were reported as unresolved, but other events resolved. The incidences of adverse events leading to treatment discontinuation were 14.3% (9 of 63 subjects) in the 45 mg single-dose group, 1.6% (1 of 64 subjects) in the 90 mg single-dose group, 1.6% (1 of 63 subjects) in the 45 mg multiple-dose group, 1.6% (1 of 62 subjects) in the 90 mg multiple-dose group, and 3.0% (2 of 67 subjects) in the placebo group, and those reported by ≥2 subjects were psoriasis (2 subjects in the 45 mg single-dose group, 2 subjects in the placebo group).

The incidences of adverse drug reactions were 74.6% (47 of 63 subjects) in the 45 mg single-dose group, 68.8% (44 of 64 subjects) in the 90 mg single-dose group, 63.5% (40 of 63 subjects) in the 45 mg multiple-dose group, 48.4% (30 of 62 subjects) in the 90 mg multiple-dose group, 24.5% (12 of 49

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subjects) in the placebo→90 mg (after Week 20) group, and 46.3% (31 of 67 subjects) in the placebo group (through Week 20), and those reported by ≥5% of subjects in any group were as shown in Table 17.

Table 17. Adverse drug reactions reported by ≥5% of subjects in any group

Preferred terms	Placebo (Weeks 0-20)	Placebo→90mg (after Week 20)	45 mg single dose	90 mg single dose	45 mg multiple doses	90 mg multiple doses
Nasopharyngitis	5 (7.5)	0	5 (7.9)	7 (10.9)	3 (4.8)	5 (8.1)
Upper respiratory tract infection	4 (6.0)	0	7 (11.1)	5 (7.8)	6 (9.5)	3 (4.8)
Urinary tract infection	0	0	3 (4.8)	1 (1.6)	4 (6.3)	3 (4.8)
Arthralgia	0	2 (4.1)	5 (7.9)	3 (4.7)	0	3 (4.8)
Myalgia	0	0	4 (6.3)	1 (1.6)	0	1 (1.6)
Arthritis	4 (6.0)	0	1 (1.6)	1 (1.6)	0	0
Pruritus	1 (1.5)	0	7 (11.1)	3 (4.7)	1 (1.6)	2 (3.2)
Headache	8 (11.9)	0	12 (19.0)	9 (14.1)	0	10 (16.1)
Diarrhoea	0	0	2 (3.2)	0	4 (6.3)	1 (1.6)
Nausea	2 (3.0)	0	1 (1.6)	3 (4.7)	2 (3.2)	4 (6.5)

n (%)

4.(ii).A.(2).4) Phase II clinical study (5.3.5.4.1, C0743T10 [December 2005 to September 2007])

A placebo-controlled, randomized, double-blind study was conducted in patients with active psoriatic arthritis (Target sample size of 140 [70 subjects per group]) to evaluate the efficacy and safety of ustekinumab.

In Group I (ustekinumab→placebo group), 90 mg[19] of ustekinumab at Weeks 0, 1, 2, and 3 and placebo at Weeks 12 and 16 were to be administered subcutaneously. In Group II (placebo→ustekinumab group), placebo at Weeks 0, 1, 2, and 3 and 90 mg[19] of ustekinumab at Weeks 12 and 16 were to be administered subcutaneously. Subjects were followed for efficacy and safety through Week 36.

All of the 146 subjects treated (76 subjects in the ustekinumab→placebo group, 70 subjects in the placebo→ustekinumab group) were included both in the safety and primary efficacy populations.

The primary efficacy endpoint of the ACR 20 response rate at Week 12 was 42.1% (32 of 76 subjects) in the ustekinumab group, which was significantly higher than 14.3% (10 of 70 subjects) in the placebo group ($P < 0.001$).

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 60.5% (46 of 76 subjects) (107 events) in the ustekinumab group and 62.9% (44 of 70 subjects) (89 events) in the placebo group. No deaths were reported. The incidences of serious adverse events were 0% (0 of 76 subjects) (0 events) in the ustekinumab group and 4.3% (3 of 70 subjects) (3

[19] During this clinical study, it was revealed that the vials of another study drug that was not used in this study contained particulate matters. Since the lyophilized formulation of ustekinumab was also filled at the same site over the same period of time, as a precautionary measure to ensure subject's safety, the prepared solution for injection was filtered. The volume of the filtered solution for injection was approximately 0.70 mL (corresponding to 63 mg of ustekinumab). In Group I, 59 of 76 subjects received the filtered solution (63 mg of ustekinumab) for all 4 doses and 3 of the remaining 17 subjects received the filtered solution (63 mg of ustekinumab) for at least one of the 4 doses. Of 70 subjects in Group II, 57 subjects at Week 12 and 55 subjects at Week 16 received the filtered solution (63 mg of ustekinumab).

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events) (myocardial infarction, gastric ulcer haemorrhage, chest pain) in the placebo group and although a causal relationship to study drug could not be denied for all events, the outcomes of all events were reported as resolved. The incidences of adverse events leading to treatment discontinuation were 1.3% (1 of 76 subjects) (1 event) (pregnancy) in the ustekinumab group and 5.7% (4 of 70 subjects) (4 events) (psoriatic arthropathy [2 events], chest pain [1 event], psoriasis [1 event]) in the placebo group, and a causal relationship to study drug could not be denied for 1 event of chest pain and 1 event of psoriatic arthropathy in the placebo group and the outcome of 1 event of psoriasis in the placebo group was reported as unresolved, but other events all resolved.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 36 were 76.3% (58 of 76 subjects) (204 events) in the ustekinumab→placebo group and 63.2% (36 of 57 subjects) (90 events) in the placebo→ustekinumab group[20]. No deaths were reported. The incidences of serious adverse events from Week 12 through Week 36 were 7.9% (6 of 76 subjects) (10 events) in the ustekinumab group (including subjects crossed over from placebo to ustekinumab) and 1.8% (1 of 57 subjects) (1 event) (pelvic mass) in the placebo→ustekinumab group (a subject who did not receive ustekinumab), and a causal relationship to study drug could not be denied for all events, but the outcomes of all events except for haemorrhagic stroke (1 subject) were reported as resolved. The incidence of adverse events leading to treatment discontinuation was 3.9% (3 of 76 subjects) (3 events) (abdominal pain; basal cell carcinoma; and haemorrhagic stroke, 1 subject each) in the ustekinumab group and a causal relationship to study drug could not be denied for all events and the outcomes of all events except for haemorrhagic stroke (1 subject) were reported as resolved.

The incidences of adverse drug reactions through Week 36 were 55.3% (42 of 76 subjects) (111 events) in the ustekinumab→placebo group and 45.6% (26 of 57 subjects) (61 events) in the placebo→ustekinumab group and those reported by ≥5% of subjects in any group were as shown in Table 18.

Table 18. Adverse drug reactions reported by ≥5% of subjects in any group

Preferred terms	Placebo (Weeks 0-12)	Placebo→Ustekinumab (Weeks 12-36)	Ustekinumab (Weeks 0-36)
Upper respiratory tract infection	4 (5.7)	5 (8.8)	7 (9.2)
Nasopharyngitis	3 (4.3)	3 (5.3)	6 (7.9)
Influenza	4 (5.7)	1 (1.8)	1 (1.3)
Diarrhoea	1 (1.4)	1 (1.8)	4 (5.3)
Nausea	0	3 (5.3)	2 (2.6)
Alanine aminotransferase increased	1 (1.4)	1 (1.8)	4 (5.3)
Headache	3 (4.3)	1 (1.8)	4 (5.3)

n (%)

4.(ii).A.(2).5) Phase III clinical study (5.3.5.1.3, C0743T08 [December 2005 to ongoing (data cut-off of March 2009)])

A placebo-controlled, randomized, double-blind study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 750 [250 subjects per group]) to evaluate the efficacy

[20] From Week 12 through Week 36, after crossover to ustekinumab.

and safety of ustekinumab and the interim report (through Week 152) (March 2009) of the study was submitted.

Forty-five or 90 mg of ustekinumab or placebo was to be administered subcutaneously according to Figure 2. A long-term extension period began at Week 52 and subjects were to continue to receive the same dose and schedule of ustekinumab that they were receiving at Week 52. Subjects randomized to placebo at Week 40 were to begin retreatment with ustekinumab every 12 weeks at loss of therapeutic effect as assessed by the PASI score.

In Study T04, the PASI 75 response rates at Week 12 in the 45 mg (single dose), 90 mg (single dose), 180 mg (45 mg/week × 4), and 360 mg (90 mg/week × 4) groups were 51.6%, 59.4%, 67.2%, and 81.3%, respectively, and a dose response relationship was observed with approximately 10% increments in PASI 75 response rate observed with every doubling in exposure between 45 mg and 360 mg. Thus, for foreign phase III studies (Studies T08 and T09), "45 or 90 mg of ustekinumab subcutaneously administered at Weeks 0 and 4" corresponding to the medium exposures tested in Study T04 (90 mg and 180 mg) was selected as the initial dosing regimen. Since efficacy peaked at around Week 12 in Study T04, the initial dosing regimen followed by the same dose every 12 weeks was proposed.

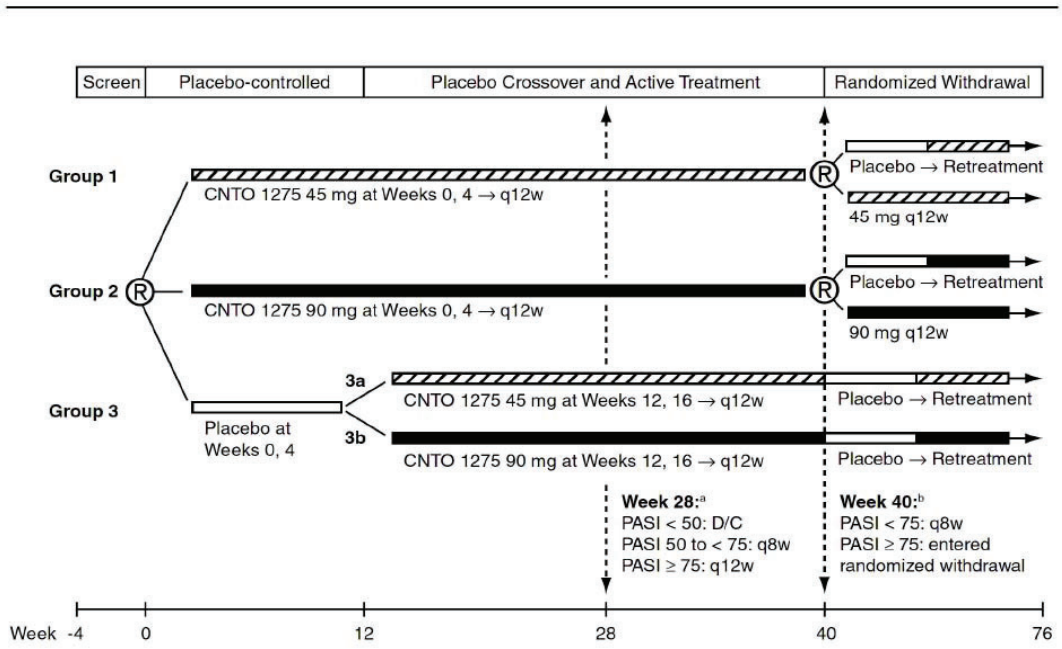


Figure 2. Study design and dosing schedule for Foreign Study T08
Group 1: 45 mg group, Group 2: 90 mg group, Group 3: placebo group, D/C: discontinuation, Ⓡ: randomization, q8w: every 8 weeks, q12w: every 12 weeks, CNTO 1275: ustekinumab
a: At Week 28, in all Groups, nonresponders discontinued study drug, partial responders began q8w dosing, and responders continued q12w dosing.
b: At Week 40, responders to q12w dosing in Groups 1 and 2 were randomized to either placebo or continued q12w ustekinumab (at their original dose) and subjects in Group 3 received placebo. At loss of therapeutic effect, subjects receiving placebo began retreatment (at their dosing regimen prior to Week 40). In all Groups, nonresponders or partial responders began q8w dosing. Subjects receiving q8w dosing continued q8w dosing.

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The primary efficacy population included 766 randomized subjects (45 mg group [Group 1 as in Figure 2] 255 subjects; 90 mg group [Group 2 as in Figure 2] 256 subjects; placebo group [Group 3a or 3b as in Figure 2] 255 subjects) while 765 subjects, excluding 1 subject who did not receive study drug (90 mg group), were included in the safety population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 (%) was as shown in Table 19 and the response rate was significantly higher in the ustekinumab groups compared to the placebo group ($P < 0.001$, pairwise comparisons using the Cochran-Mantel-Haenszel χ^2 test). The secondary endpoints of the PASI 50 response rate and the PASI 90 response rate were as shown in Table 19.

Table 19. PASI response rate at Week 12

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
PASI 50 response rate	10.2 (26/255)	83.5 (213/255)	85.9 (220/256)
PASI 75 response rate	3.1 (8/255)	67.1 (171/255)	66.4 (170/256)
PASI 90 response rate	2.0 (5/255)	41.6 (106/255)	36.7 (94/256)

% (n)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 57.6% (147 of 255 subjects) (302 events) in the 45 mg group, 51.4% (131 of 255 subjects) (269 events) in the 90 mg group, and 48.2% (123 of 255 subjects) (224 events) in the placebo group. No deaths were reported. Serious adverse events were reported by 2 subjects in the 45 mg group (cerebrovascular accident; and hypertension, 1 subject each), 4 subjects in the 90 mg group (herpes zoster disseminated; cellulitis; coronary artery disease; and psoriasis, 1 subject each), and 2 subjects in the placebo group (psychotic disorder; and pneumonia, 1 subject each), and a causal relationship to study drug could not be denied for any of these events except for coronary artery disease, but the outcomes of all events were reported as resolved. The incidences of adverse events leading to treatment discontinuation were 0.4% (1 of 255 subjects) (cerebrovascular accident) in the 45 mg group, 1.6% (4 of 255 subjects) (herpes zoster disseminated; cellulitis; pregnancy; and dyspepsia, 1 subject each) in the 90 mg group, and 2.4% (6 of 255 subjects) (psoriasis [2 subjects], dermatitis exfoliative [2 subjects], psychotic disorder [1 subject], rash generalised [1 subject]) in the placebo group, and a causal relationship to study drug could not be denied for any of these events except for pregnancy, but the outcomes of all events except for pregnancy were reported as resolved.

The incidences of adverse drug reactions were 35.3% (90 of 255 subjects) (163 events) in the 45 mg group, 30.6% (78 of 255 subjects) (162 events) in the 90mg group, and 27.1% (69 of 255 subjects) (125 events) in the placebo group and those reported by ≥2% of subjects in any group were as shown in Table 20.

Table 20. Adverse drug reactions reported by ≥2% of subjects in any group (through Week 12)

Preferred terms	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
Upper respiratory tract infection	9 (3.5)	11 (4.3)	12 (4.7)
Nasopharyngitis	8(3.1)	9 (3.5)	9 (3.5)
Headache	5(2.0)	12 (4.7)	11 (4.3)
Dizziness	1 (0.4)	5 (2.0)	3 (1.2)
Fatigue	3 (1.2)	4 (1.6)	6 (2.4)
Injection site erythema	2 (0.8)	0	7 (2.7)
Arthralgia	6 (2.4)	4 (1.6)	6 (2.4)

n (%)

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The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 152 were 92.1% (348 of 378 subjects) (2481 events) in the 45 mg group[21] and 90.9% (341 of 375 subjects) (2400 events) in the 90 mg group[22]. Two subjects in the placebo→90 mg group (respiratory failure, pneumonia, chronic hepatic failure, and colitis; and completed suicide) and 1 subject in the 90 mg group (intestinal perforation) died, but a causal relationship to study drug was denied for all cases. The incidences of serious adverse events were 7.9% (30 of 378 subjects) in the 45 mg group and 10.1% (38 of 375 subjects) in the 90 mg group, and those reported by ≥2 subjects in either group were coronary artery disease (7 subjects in the 90 mg group), prostate cancer (3 subjects in the 45 mg group), cellulitis (2 subjects in the 90 mg group), osteomyelitis (2 subjects in the 90 mg group), myocardial infarction (2 subjects in the 90 mg group), and cerebrovascular accident (2 subjects in the 45 mg group). The incidences of adverse events leading to treatment discontinuation from Week 0 through Week 152 were 6.9% (26 of 378 subjects) in the 45 mg group and 6.4% (24 of 375 subjects) in the 90 mg group.

The incidences of adverse drug reactions were 62.4% (236 of 378 subjects) (1116 events) in the 45 mg group and 62.9% (236 of 375 subjects) (1073 events) in the 90 mg group and those reported by ≥2% of subjects in either group were as shown in Table 21.

Table 21. Adverse drug reactions reported by ≥2% of subjects in either group (through Week 152)

Preferred terms	Ustekinumab 45 mg	Ustekinumab 90 mg
Nasopharyngitis	35 (9.3)	45 (12.0)
Upper respiratory tract infection	69 (18.3)	64 (17.1)
Sinusitis	21 (5.6)	18 (4.8)
Influenza	17 (4.5)	16 (4.3)
Gastroenteritis	19 (5.0)	14 (3.7)
Bronchitis	16 (4.2)	15 (4.0)
Pharyngitis	9 (2.4)	9 (2.4)
Urinary tract infection	10 (2.6)	7 (1.9)
Arthralgia	27 (7.1)	19 (5.1)
Psoriatic arthropathy	9 (2.4)	4 (1.1)
Arthritis	9 (2.4)	6 (1.6)
Back pain	9 (2.4)	12 (3.2)
Pain in extremity	6 (1.6)	8 (2.1)
Diarrhoea	8 (2.1)	14 (3.7)
Oropharyngeal pain	6 (1.6)	9 (2.4)
Nasal congestion	5 (1.3)	8 (2.1)
Headache	29 (7.7)	22 (5.9)
Dizziness	11 (2.9)	11 (2.9)
Injection site erythema	14 (3.7)	19 (5.1)
Fatigue	15 (4.0)	10 (2.7)
Night sweats	9 (2.4)	7 (1.9)
Cough	12 (3.2)	11 (2.9)
Alanine aminotransferase increased	7 (1.9)	8 (2.1)
Insomnia	8 (2.1)	8 (2.1)
Hypertension	17 (4.5)	16 (4.3)

n (%)

[21] A group of subjects who received 45 mg of ustekinumab by Week 152 (Group 1 and Group 3a). After Week 12 (after crossover to ustekinumab) for Group 3a.

[22] A group of subjects who received 90 mg of ustekinumab by Week 152 (Group 2 and Group 3b). After Week 12 (after crossover to ustekinumab) for Group 3b.

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4.(ii).A.(2).6) Phase III study (5.3.5.1.4, C0743T09 [March 2006 to ongoing (data cut-off of August 2008)])

A placebo-controlled, randomized, double-blind study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 1200 [400 subjects per group]) to evaluate the efficacy and safety of ustekinumab and the interim report (through Week 100) (August 2008) of the study was submitted.

Forty-five or 90 mg of ustekinumab or placebo was to be administered subcutaneously according to Figure 3. A long-term extension period began at Week 52 and after the unblinding, adjustment of each subject's dosing regimen was allowed at the investigator's discretion. The duration of treatment was up to 264 weeks.

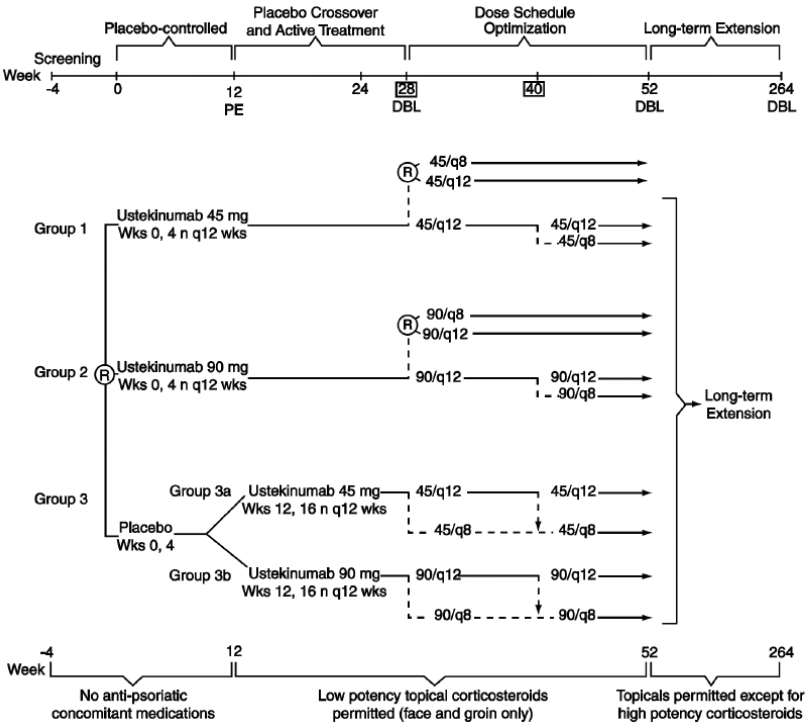


Figure 3. Study design and dosing schedule for Foreign Study T09
Group 1: 45 mg group, Group 2: 90 mg group, Group 3: placebo group, Ⓡ: randomization, PE: primary endpoint, DBL: database lock, q8: every 8 weeks, q12: every 12 weeks.
At Week 28, in all Groups, nonresponders discontinued study treatment. In Groups 1 and 2, partial responders were randomized to either q8wk or q12wk dosing. In Group 3, partial responders began q8wk dosing.
At Week 40, among responders at Week 28 in all Groups, nonresponders and partial responders began q8wk dosing.

The safety population and the primary efficacy population included 1230 randomized subjects (45 mg group [Group 1 as in Figure 3] 409 subjects; 90 mg group [Group 2 as in Figure 3] 411 subjects; placebo group [Group 3a or 3b as in Figure 3] 205 subjects each).

The primary efficacy endpoint of the PASI 75 response rate (%) at Week 12 was as shown in Table 22 and the response rate was significantly higher in the ustekinumab groups compared to the placebo

group ($P < 0.001$, pairwise comparisons using the Cochran-Mantel-Haenszel χ^2 test). The secondary endpoints of the PASI 50 resposne rate and the PASI 90 response rate were as shown in Table 22.

Table 22. PASI response rates at Week 12

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
PASI 50 response rate	10.0 (41/410)	83.6 (342/409)	89.3 (367/411)
PASI 75 response rate	3.7 (15/410)	66.7 (273/409)	75.7 (311/411)
PASI 90 response rate	0.7 (3/410)	42.3 (173/409)	50.9 (209/411)

% (n)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 53.1% (217 of 409 subjects) (402 events) in the 45 mg group, 48.7% (200 of 411 subjects) (408 events) in the 90 mg group, and 49.8% (204 of 410 subjects) (365 events) in the placebo group. The incidences of serious adverse events were 2.0% (8 of 409 subjects) (intervertebral disc protrusion [2 subjects], angina pectoris; nephrolithiasis; seroma; dactylitis; sciatica; and clavicle fracture, 1 subject each) in the 45 mg group, 1.2% (5 of 411 subjects) (congestive cardiomyopathy; meningioma benign; cellulitis; alcohol withdrawal syndrome; and hypertension, palpitations, ventricular extrasystoles, and vertigo, 1 subject each) in the 90 mg group, and 2.0% (8 of 410 subjects) (cellulitis [2 subjects], hepatic neoplasm malignant and ascites; asthma; cervicobrachial syndrome; chest pain; psoriatic arthropathy; and pityriasis rubra pilaris, 1 subject each) in the placebo group and a causal relationship to study drug could not be denied for any of these events except for intervertebral disc protrusion (2 subjects), angina pectoris, nephrolithiasis, and seroma in the 45 mg group, meningioma benign and alcohol withdrawal syndrome in the 90 mg group, and hepatic neoplasm malignant and ascites; cervicobrachial syndrome; chest pain; and pityriasis rubra pilaris in the placebo group and the outcomes of all events were reported as resolved except for congestive cardiomyopathy (death) in the 90 mg group and hepatic neoplasm malignant and ascites; and psoriatic arthropathy (all unresolved) in the placebo group. The incidences of adverse events leading to treatment discontinuation were 0.2% (1 of 409 subjects) (1 event) (neutropenia) in the 45 mg group, 1.5% (6 of 411 subjects) (10 events) (pneumonia; basal cell carcinoma; hepatitis; meningioma benign; hypertension, palpitations, ventricular extrasystoles, and vertigo; and alcohol abuse and alcohol withdrawal syndrome, 1 subject each) in the 90 mg group, and 1.7% (7 of 410 subjects) (7 events) (psoriasis [2 subjects], pustular psoriasis; cellulitis; pregnancy; ascites; and psoriatic arthropathy, 1 subject each) in the placebo group, and a causal relationship to study drug could not be denied for all events except for pregnancy and ascites in the placebo group and basal cell carcinoma; meningioma benign; and alcohol abuse and alcohol withdrawal syndrome in the 90 mg group and the outcomes of all events except for ascites, pustular psoriasis, and psoriatic arthropathy in the placebo group were reported as resolved.

The incidences of adverse drug reactions (including abnormal laboratory test values) were 34.5% (141 of 409 subjects) in the 45 mg group, 32.8% (135 of 411 subjects) in the 90 mg group, and 29.5% (121 of 410 subjects) in the placebo group and those reported by ≥2% of subjects in any group were as shown in Table 23.

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Table 23. Adverse drug reactions reported by ≥2% of subjects in any group (through Week 12)

Preferred terms	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
Nasopharyngitis	18 (4.4)	15 (3.7)	13 (3.2)
Upper respiratory tract infection	8 (2.0)	10 (2.4)	7 (1.7)
Diarrhoea	8 (2.0)	7 (1.7)	10 (2.4)
Headache	12 (2.9)	19 (4.6)	13 (3.2)
Fatigue	8 (2.0)	11 (2.7)	10 (2.4)
Arthralgia	5 (1.2)	12 (2.9)	8 (1.9)

n (%)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 100 were 90.4% (548 of 606 subjects) (2883 events) in the 45 mg group[23] and 90.4% (548 of 606 subjects) (2956 events) in the 90 mg[24] group. One subject in the placebo→45 mg group (aspiration), 1 subject in the placebo→90 mg group (metastatic renal cancer), and 2 subjects in the 90 mg group (shock, congestive cardiomyopathy) died and a causal relationship to study drug was denied for all events except for congestive cardiomyopathy. The incidences of serious adverse events were 10.1% (61 of 606 subjects) in the 45 mg group and 9.2% (56 of 606 subjects) in the 90 mg group and those reported by ≥2 subjects in either group were as shown in Table 24. The incidences of serious adverse events for which a causal relationship to study drug could not be denied were 2.5% (15 of 606 subjects) in the 45 mg group and 2.6% (16 of 606 subjects) in the 90 mg group. The incidences of adverse events leading to treatment discontinuation were 3.3% (20 of 606 subjects) in the 45 mg group and 5.4% (33 of 606 subjects) in the 90 mg group.

The incidences of adverse drug reactions (including abnormal laboratory test values) were 62.9% (381 of 606 subjects) in the 45 mg group and 63.7% (386 of 606 subjects) in the 90 mg group, and those reported by ≥2% of subjects in either group were as shown in Table 25.

Table 24. Serious adverse events reported by ≥2 subjects in either group (through Week 100)

Preferred terms	Ustekinumab 45 mg	Ustekinumab 90 mg
Coronary artery disease	4 (0.7)	1 (0.2)
Angina unstable	2 (0.3)	2 (0.3)
Myocardial infarction	2 (0.3)	1 (0.2)
Prostate cancer	1 (0.2)	2 (0.3)
Cellulitis	2 (0.3)	1 (0.2)
Diverticulitis	1 (0.2)	2 (0.3)
Abdominal pain	2 (0.3)	0
Chest pain	2 (0.3)	6 (1.0)
Nephrolithiasis	3 (0.5)	1 (0.2)
Renal colic	1 (0.2)	2 (0.3)
Intervertebral disc protrusion	4 (0.7)	0

n (%)

Table 25. Adverse drug reactions reported by ≥2% of subjects in either group (through Week 100)

Preferred terms	Ustekinumab 45 mg	Ustekinumab 90 mg
Nasopharyngitis	93 (15.3)	101 (16.7)
Upper respiratory tract infection	96 (15.8)	90 (14.9)
Influenza	34 (5.6)	38 (6.3)
Bronchitis	28 (4.6)	23 (3.8)
Sinusitis	20 (3.3)	27 (4.5)
Gastroenteritis	23 (3.8)	21 (3.5)
Pharyngitis	7 (1.2)	12 (2.0)
Urinary tract infection	9 (1.5)	13 (2.1)
Oral herpes	13 (2.1)	7 (1.2)

[23] A group of subjects who received 45 mg of ustekinumab by Week 100 (Group 1 and Group 3a).

[24] A group of subjects who received 90 mg of ustekinumab by Week 100 (Group 2 and Group 3b).

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Back pain	19 (3.1)	25 (4.1)
Arthralgia	33 (5.4)	36 (5.9)
Myalgia	11 (1.8)	14 (2.3)
Pain in extremity	13 (2.1)	10 (1.7)
Skeletal muscle pain	12 (2.0)	6 (1.0)
Chest pain	4 (0.7)	17 (2.8)
Diarrhoea	25 (4.1)	23 (3.8)
Pruritus	11 (1.8)	16 (2.6)
Night sweats	5 (0.8)	14 (2.3)
Fatigue	24 (4.0)	20 (3.3)
Injection site erythema	22 (3.6)	25 (4.1)
Headache	46 (7.6)	38 (6.3)
Dizziness	10 (1.7)	16 (2.6)
Cough	22 (3.6)	27 (4.5)
Pharyngolaryngeal pain	14 (2.3)	20 (3.3)
Hypertension	25 (4.1)	29 (4.8)

n (%)

4.(ii).B Outline of the review

4.(ii).B.(1) Efficacy

4.(ii).B.(1).1) Efficacy in the treatment of psoriasis vulgaris and plaque psoriasis in psoriatic arthritis

PMDA concludes that based on the submitted study data, the efficacy of ustekinumab in the treatment of psoriasis vulgaris and plaque psoriasis in psoriatic arthritis has been demonstrated.

4.(ii).B.(1).2) Efficacy of ustekinumab in reducing joint symptoms of psoriatic arthritis

While the treatment of joint symptoms as well as skin symptoms is considered important in psoriatic arthritis, pain VAS assessment only was performed in Japanese Study JPN-02 and the efficacy of ustekinumab in reducing joint symptoms has not been confirmed overseas either. PMDA asked the applicant to explain their view on the expected degree of efficacy of ustekinumab in reducing joint symptoms.

The applicant explained as follows:

In Japanese Study JPN-02, 22 subjects who were confirmed by the investigator or sub-investigator to have joint symptoms at Week 0 (3 subjects in the placebo group, 6 subjects in the 45 mg group, 13 subjects in the 90 mg group) were assessed for pain VAS score. As a result, the median changes from baseline at Week 12 (mean ± SD) were 1.0 (8.0 ± 13.00) in the placebo group, -41.0 (-38.5 ± 28.93) in the 45 mg group, and -10.0 (-9.3 ± 18.23) in the 90 mg group, and ustekinumab tended to reduce joint pain, though the number of subjects assessed was small. In a foreign phase II clinical study that evaluated the efficacy of ustekinumab in reducing the symptoms and signs of arthritis in patients with active psoriatic arthritis (Study T10), the primary endpoint of the ACR 20 response rate at Week 12 was significantly higher in the ustekinumab group (42.1% [32 of 76 subjects]) compared to the placebo group (14.3% [10 of 70 subjects]) ($P < 0.001$, Cochran-Mantel-Haenszel $\chi 2$ test), suggesting the efficacy of ustekinumab in reducing joint symptoms. These results are not substantially different from the results from adalimumab or infliximab foreign phase II and III studies in patients with active psoriatic arthritis (Table 26).

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Table 26. Comparison of efficacy of ustekinumab vs. other biologics
based on foreign placebo-controlled, double-blind studies in patients with psoriatic arthritis

Summary of study											
Product	Ustekinumab			Infliximab				Adalimumab			
Study ID	Foreign phase II clinical study (C0743T10)			Phase II clinical study (IMPACT)		Phase III clinical study (IMPACT2)		Phase III clinical study (Study M02-518)		Phase III clinical study (Study M02-570)	
Main dosing regimen	ustekinumab 90 mg (63 mg)* or placebo subcutaneously administered at Weeks 0, 1, 2, and 3 and then crossover to placebo or ustekinumab 90 mg (63 mg) subcutaneously administered at Weeks 12 and 16			infliximab 5 mg/kg or placebo given as an intravenous infusion at Weeks 0, 2, 6, and 14		infliximab 5 mg/kg or placebo given as an intravenous infusion at Weeks 0, 2, 6, 14, and 22		adalimumab 40 mg or placebo subcutaneously administered every other week		adalimumab 40 mg or placebo subcutaneously administered every other week	
Primary endpoint	ACR 20 response rate (Week 12)			ACR 20 response rate (Week 16)		ACR 20 response rate (Week 14)		ACR 20 response rate (Week 12)		ACR 20 response rate (Week 12)	
Study results											
Treatment group	Placebo	Ustekinumab 90 mg (63 mg)	Placebo →90 mg (63 mg)[a]	Placebo	infliximab 5 mg/kg	Placebo	infliximab 5 mg/kg	Placebo	adalimumab 40 mg	Placebo	adalimumab 40 mg
Number of subjects	70	76	55	52	52	100	100	162	151	49	51
ACR 20 response rate	14.3%	42.1%	50.9%	9.6%	65.4%	11.0%	58.0%	14%	58%	16%	39%
Pain VAS score (SD)	-13.17 (62.141) [b]	21.38 (65.579) [b]	29.23 (49.817) [b]	-8.7 (7.8) [b]	53.7 (7.7) [b]	-11.8 (109.8) [b]	39.6 (56.1) [b]	—	—	0.2 (23.1) [c]	-15.4 (25.6) [c]

a: Assessment at Week 24 (12 weeks after crossover to ustekinumab) for subjects crossed over from placebo to ustekinumab at Week 12,
b: mean percent improvement (SD), c: mean change (SD)
* During this clinical study, it was revealed that the vials of another study drug that was not used in this study contained particulate matters. Since the lyophilized formulation of ustekinumab used in this study was also filled at the same site over the same period of time, as a precautionary measure to ensure subject's safety, the prepared solution for injection was filtered (pore size, 0.22 μm). The volume of the filtered solution for injection was approximately 0.70 mL (corresponding to 63 mg of ustekinumab).

Furthermore, in Study T10 and foreign studies of adalimumab and infliximab, changes in pain VAS score were measured as an ACR core set variable. As a result, as shown in Table 26, improvement in joint pain as measured by pain VAS score as well as improvement in joint symptoms as measured by the primary endpoint of the ACR 20 response rate was observed simultaneously in all studies. Based on the above, though pain VAS assessment only was performed in Japanese Study JPN-02, the efficacy of ustekinumab in reducing joint symptoms can be expected also in Japanese patients with psoriatic arthritis.

The applicant also responded as follows:
Two foreign phase III studies to confirm the efficacy of ustekinumab (45 mg and 90 mg) in improving the symptoms and signs of arthritis and preventing joint structural damage progression in patients with active psoriatic arthritis are currently ongoing.

In Japanese Study JPN-02, subjects with joint symptoms at Week 0, regardless of a diagnosis of psoriatic arthritis, were assessed for pain VAS score. PMDA asked the applicant to also explain the results from subjects diagnosed with psoriatic arthritis.

The applicant explained as follows:

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Usually, patients who develop psoriatic arthritis have skin symptoms of psoriasis first, followed by joint symptoms several years later and the statistics of psoriasis patients in Japan report that only 1.0% of the patients are diagnosed with psoriatic arthritis at the first visit (Hashimoto Y. *Dermatology Practice 16 Psoriasis*. 2004;215-9). Based on patients registered with the Japanese Society for Psoriasis Research from 1999 to 2002 (4 years), 2.0% of the patients were diagnosed with psoriatic arthritis at the first visit while 7.6% of the patients had joint symptoms. Taking account of these findings, subjects who were confirmed by the investigator or sub-investigator to have joint symptoms, regardless of a diagnosis of psoriatic arthritis, were assessed for pain VAS score in Japanese Study JPN-02. Of 14 subjects with a diagnosis of psoriatic arthritis enrolled in Study JPN-02, 12 subjects had joint symptoms at Week 0 and were assessed for pain VAS score (1 subject in the placebo group, 4 subjects in the 45 mg group, 7 subjects in the 90 mg group). In these 12 subjects, the percent improvement in pain VAS score from baseline to Week 12 was -2.8% in the 1 subject in the placebo group and the median values (mean ± SD) in the 45 mg and 90 mg groups were 53.00% (27.19 ± 78.451) and 41.67% (29.88 ± 40.205), respectively. Though the number of subjects assessed was limited, like the results from 22 subjects with joint symptoms, these results have suggested that ustekinumab improves joint pain.

PMDA considers as follows:

As there are a limited number of patients with psoriatic arthritis in Japan, it is understandable that it was difficult to conduct a Japanese clinical study to confirm the efficacy of ustekinumab in reducing joint symptoms. Meanwhile, Japanese Study JPN-02 should have been designed to allow for certain assessment of joint symptoms as well. For example, patients diagnosed with psoriatic arthritis should have been enrolled in the study and balanced across treatment groups for assessment of joint symptoms and the ACR response rates etc. should have also been assessed with a view to comparison with foreign study data. On the other hand, the results from a foreign phase II study, though not a confirmatory study, have suggested the efficacy of ustekinumab in reducing joint symptoms as assessed by the ACR criteria, the results from Japanese Study JPN-02 have shown a trend toward improvement in pain VAS score though in a small number of subjects, and foreign clinical studies of ustekinumab and existing biologics have suggested similar trends in the ACR 20 response rate and pain VAS score. Taking account of these findings, the efficacy of ustekinumab in reducing joint symptoms can be expected also in Japanese patients with psoriatic arthritis and there should be no major problems in the assessment of joint symptoms in the Japanese clinical study. However, as data in Japanese patients with psoriatic arthritis are very limited, data concerning joint symptoms should be obtained wherever possible via post-marketing surveillance, arranging for patients who have mainly joint symptoms and see rheumatologists etc. to be assessed also for disease activity as measured by the ACR core set or DAS, and the information including foreign data on the inhibition of structural damage progression etc., which will become available in future, should be provided appropriately to healthcare providers in clinical settings.

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4.(ii).B.(2) Dosage and administration

4.(ii).B.(2).1) Dosage and administration

4.(ii).B.(2).1).(a) Usual dose

In Japanese Study JPN-02, although the primary endpoint of the PASI 75 response rate at Week 12 tended to be higher in the 90 mg group (67.7%) compared to the 45 mg group (59.4%), the PASI 50 response rate was almost the same in the 45 mg group (82.8%) and the 90 mg group (83.9%), which indicated that both dose levels of ustekinumab can achieve clinically significant improvement in skin lesions in most patients, etc. Thus, a usual dose of 45 mg of ustekinumab has been proposed.

PMDA concluded that there is no particular problem with the proposed usual dose of 45 mg of ustekinumab, which can be expected to produce a clinical response in most psoriasis patients.

4.(ii).B.(2).1).(b) An increased dose of 90 mg

In Foreign Studies T08 and T09, serum ustekinumab concentrations decreased with increasing body weight and the PASI 75 response rate also tended to be lower, and there were differences in efficacy between the 45 mg and 90 mg groups in subjects weighing >100 kg, and the PASI 75 response rate and the trough serum concentration of ustekinumab, etc. in subjects weighing >100 kg in the 90 mg group were comparable to those in subjects weighing ≤100 kg in the 45 mg group. On the basis of these findings, among others, in foreign countries including the US and the EU, the recommended dose of ustekinumab is 45 mg for psoriasis patients weighing ≤100 kg and 90 mg for psoriasis patients weighing >100 kg. Also in Japanese Study JPN-02, serum ustekinumab concentrations decreased with increasing body weight and the PASI 75 response rate also tended to be lower, suggesting that subjects weighing >100 kg tended to have lower serum ustekinumab concentrations. The pharmacokinetics of ustekinumab are considered similar between Japanese and foreign patients of the same body weight range and it is predicted that a dose response relationship as seen in the foreign studies occurs in subjects weighing >100 kg. Therefore, also in Japan, the following statement has been included in the proposed dosage and administration section: “A 90 mg dose may be used in patients weighing >100 kg”.

However, only 6 subjects weighing >100 kg were enrolled in the Japanese study and there is no sufficient evidence supporting the use of a 90 mg dose in this patient population. In addition, Japanese patients weighing >100 kg are uncommon. Taking account of these points, PMDA considers that the proposed dosing instruction is not appropriate.

On the other hand, in Japanese Study JPN-02, the PASI 75 response rate and PASI 90 response rate at Week 12 in the 90 mg group were 8.3% and 10.7% higher, respectively, than those in the 45 mg group and ≥10% higher response rates were observed consistently also after Week 28 and there were no major differences in safety between the two groups. Furthermore, in Study JPN-02 (at Week 28), 33.3% of subjects in the 45 mg group and 17.5% of subjects in the 90 mg group had trough serum ustekinumab concentrations less than the lower limit of quantification (0.17 μg/mL) and this

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proportion was rather high, especially in the 45 mg group, and the PASI 75 response rate in subjects with trough serum ustekinumab concentrations less than the lower limit of quantification was approximately 30% lower than that in subjects with trough serum ustekinumab concentrations of ≥0.17 μg/mL to <0.40 μg/mL [see "4.(i) Summary of clinical pharmacology studies"]. Taking account of these findings, the lack of efficacy in a certain number of subjects due to insufficient serum ustekinumab concentrations is expected at a dose of 45 mg, regardless of body weight (>100 kg). Therefore, in Japan, a dose increase should be recommended as follows: "If the effect of a 45 mg dose is insufficient, a dose of 90 mg may be used."

Since a dose increase may be attempted also in nonresponders to ustekinumab, etc., symptoms over time after the dose increase should be monitored closely and it is necessary to adequately advise against continuing high-dose ustekinumab without careful consideration in patients in whom no effects of the increased dose of ustekinumab are noted. The efficacy and safety of an increased dose of ustekinumab need to be fully investigated via post-marketing surveillance.

4.(ii).B.(2).2) Possibility of withdrawal from ustekinumab therapy etc. after remission

PMDA asked the applicant to explain their view on the possibility of withdrawal of therapy after remission with ustekinumab or the possibility of intermittent administration (treatment interruption with reintroduction as needed) etc.

The applicant explained as follows:

In Foreign Study T08, (a) responders at Week 40 (subjects with a ≥75% improvement in PASI score) were re-randomized to maintenance therapy or withdrawal of therapy and the time to loss of PASI 75 response was assessed. In subjects re-randomized to withdrawal of therapy, the PASI 75 response rate decreased over time and was 63% at Week 52 (12 weeks after treatment withdrawal) and 70.3% of the subjects had an increase in PGA score of ≥1 at Week 52 and (b) furthermore, the percent improvement in PASI score over time after treatment withdrawal in responders at Week 40 re-randomized to placebo (i.e. treatment withdrawal) was assessed according to the percent improvement in PASI score at Week 40 (≥75% to <90% [32 subjects in the 45 mg group, 45 subjects in the 90 mg group] vs. ≥90% [109 subjects in the 45 mg group, 134 subjects in the 90 mg group]). The mean and median percent improvements in PASI scores were less than 75% at Weeks 48 to 52 in subjects with a ≥75% to <90% improvement at Week 40 and less than 75% at Week 60 even in subjects with a ≥90% improvement at Week 40, suggesting that it is not true that PASI response is maintained for a long time in subjects who showed a higher percent improvement in PASI score. Based on these results, continuous administration of ustekinumab is recommended.

PMDA considers as follows:

Given that ustekinumab is associated with the risk of serious adverse reactions, the amount of ustekinumab used should be minimized. As patients with prolonged remission etc. may be studied, a more detailed investigation concerning treatment withdrawal and intermittent administration as needed

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etc. should be performed in future. It is important to investigate symptoms over time etc. in patients after treatment withdrawal and patients retreated after withdrawal from therapy etc. and collect sufficient information, also after the product launch.

4.(ii).B.(3) Indications and clinical positioning etc.

4.(ii).B.(3).1) Indications

PMDA considers as follows:

The confirmatory study of ustekinumab was designed to enrollpatients regardless of prior medication use, etc. and was conducted on the assumption that ustekinumab would be used even as a first-line drug for patients resistant to local therapy (i.e. as an equal option to phototherapy or conventional systemic therapy such as cyclosporine and etretinate). Psoriasis is not generally a fatal disease while ustekinumab, as with adalimumab and infliximab (other biologics approved for psoriasis), increases the risk of serious infections etc. which may run a fatal course, and the long-term safety of ustekinumab including the risk of malignancy has not fully been elucidated. Taking account of these points, it is not appropriate to position ustekinumab as an equal option to phototherapy or conventional systemic therapy and ustekinumab should rather be positioned as a treatment, like the approved biologics, for patients who have had an inadequate response or intolerance to phototherapy or conventional systemic therapy, etc.

PMDA asked the applicant to present the results of subgroup analyses of patients who were considered to have an inadequate response to phototherapy or cyclosporine or etretinate. As described below, the applicant responded that there were no major differences in the efficacy and safety of ustekinumab between the subgroups and the overall population.

Although the response to prior therapy for psoriasis was not reported in Japanese Study JPN-02, given that the study included patients with moderate to severe psoriasis, it is inferred that the majority of the subjects failed to respond adequately to prior therapy. Thus, subgroup analyses were performed according to previous experience with cyclosporine, etretinate or phototherapy. As a result, regarding efficacy, the PASI 75 response rates among subjects with previous experience with cyclosporine, etretinate, or phototherapy were 59.6% (31 of 52 subjects) in the 45 mg group, 67.2% (39 of 58 subjects) in the 90 mg group, and 0% (0 of 25 subjects) in the placebo group, which were almost comparable to those in the overall population (59.4% in the 45 mg group, 67.7% in the 90 mg group, 6.5% in the placebo group). Also when subgroups were analyzed according to previous experience with each of cyclosporine, etretinate, and phototherapy, there were no major differences in the results between each of the subgroups and the overall population, though the number of subjects of each subgroup was small. Regarding safety, overall adverse events, serious adverse events, adverse events leading to treatment discontinuation, and serious infections were analyzed according to previous experience with each of cyclosporine, etretinate, and phototherapy. As a result, the incidences of adverse events by treatment group were similar, regardless of previous experience with each of these therapies.

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Furthermore, as the response to prior therapy was reported in Foreign Studies T08 and T09, a subgroup analysis of subjects who had an inadequate response to cyclosporine, acitretin (an oral retinoid, unapproved in Japan), or phototherapy was performed. The PASI 75 response rates at Week 12 in the 45 mg, 90 mg, and placebo groups were 66.8% (181 of 271 subjects), 70.1% (162 of 231 subjects), and 2.2% (6 of 267 subjects), respectively, which were almost comparable to those in the overall population (66.9% in the 45 mg group, 72.1% in the 90 mg group, 3.5% in the placebo group). There were also no major differences in safety between the subgroup of subjects who had an inadequate response to cyclosporine, acitretin, or phototherapy and the overall population.

Based on the above, PMDA considers as follows:
The indication statement should be modified as shown below and the following statements should be included in the precautions for indications section of the package insert: ustekinumab should be used in (a) patients with a body surface area involvement of ≥10% who have had an inadequate response to conventional systemic therapy (including UV-light therapy) or (b) patients with refractory skin or joint symptoms. In addition, the use of ustekinumab should be limited to physicians who are familiar with the diagnosis and treatment of psoriasis to ensure that a correct diagnosis is made, that appropriate patients are selected, and that the proper use is complied with.

[Indications]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris, Psoriatic arthritis

Given that ustekinumab has been demonstrated to be highly effective in the treatment of plaque psoriasis etc. and that its mechanism of action is different from conventional therapy, ustekinumab is expected to play an important role in the treatment of psoriasis. In order to prevent ustekinumab from being used improperly, it is important that the use of ustekinumab is determined carefully based on its risks and benefits and that patients themselves also fully understand the risks of ustekinumab and comply with its proper use.

4.(ii).B.(3).2) Positioning of ustekinumab relative to existing biologics
While both adalimumab and infliximab (other biologics approved for the treatment of psoriasis) neutralize the biological activity of human TNF-α, ustekinumab binds to human IL-12 and IL-23 and neutralizes their biological activities. Ustekinumab has a novel mechanism of action. PMDA asked the applicant to explain their view on the positioning of ustekinumab relative to the existing biologics.

The applicant explained as follows:
No head to head efficacy studies of ustekinumab vs. adalimumab or infliximab have been performed in Japan or overseas.Adalimumab and infliximab were approved for the indication of psoriasis in

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Japan in January 2010 and there is limited clinical experience with these biologics in Japanese psoriasis patients at present. Thus, it is difficult to define the positioning of ustekinumab relative to these drugs. Compared to these drugs, ustekinumab has the following characteristics: (a) Comparison of the results of Japanese clinical studies indicates that the efficacy of ustekinumab in treating psoriatic skin lesions is as high as that of adalimumab or infliximab (Table 27), (b) The safety databases, which include Japanese and foreign data, have shown a favorable safety profile of ustekinumab and there should be no particular safety concerns about ustekinumab compared to anti-TNF agents at present, and (c) Psoriasis has a chronic nature, which often requires long-term treatment, while the effect of ustekinumab is maintained by subcutaneous injections every 12 weeks and ustekinumab requires lower dosing frequency and is easier to use, compared to adalimumab and infliximab. Furthermore, ustekinumab has a novel mechanism of action and the results from foreign phase III studies have suggested the efficacy of ustekinumab also in subjects who have discontinued other biologic therapy due to an inadequate response. There have been no safety concerns about the use of ustekinumab, even in subjects who have discontinued other biologic therapy due to intolerance (Tables 28 and 29). Taking account of these findings, ustekinumab is expected to possibly offer another therapeutic option for patients who do not respond to adalimumab or infliximab or those who cannot use adalimumab or infliximab for safety reasons.

Table 27. Comparison of efficacy of ustekinumab vs. other biologics
based on Japanese placebo-controlled, double-blind studies in psoriasis patients

Non-proprietary name	Ustekinumab		Adalimumab[a]		Infliximab[a]	
Psoriasis severity	PASI ≥12 BSA ≥10%		PASI ≥12 BSA ≥10%		PASI ≥12 BSA ≥10%	
Dosing regimen during the placebo-controlled period	45 mg, 90 mg, or placebo administered at Weeks 0 and 4		40 mg, 80 mg, or placebo administered every other week (including loading dose of 80 mg followed by 40 mg given every other week)		5 mg/kg or placebo intravenously administered at Weeks 0, 2, and 6	
Primary endpoint	PASI 75 response rate at Week 12		PASI 75 response rate at Week 16		PASI 75 response rate at Week 10	
PASI 75 response rate at the proposed or approved dosing regimen	Placebo	45 mg	Placebo	80 mg loading dose + 40 mg	Placebo	5 mg/kg
	6.5% (2/31 subjects)	59.4% (38/64 subjects)	4.3% (2/46 subjects)	62.8% (27/43 subjects)	0% (0/19 subjects)	68.6% (24/35 subjects)

a: Cited from the disclosed CTD and the package insert

Table 28. PASI 50, PASI 75, and PASI 90 response rates (Week 12) in subjects previously treated with other biologics

	Pooled data from Studies T08 and T09		
	Placebo	45 mg	90 mg
Patients who have discontinued other biologic therapy (etanercept, infliximab, adalimumab, alefacept, efalizumab) due to an inadequate response (n)	104	81	106
PASI 90 response rate	1 (1.0%)	32 (39.5%)	38 (35.8%)
PASI 75 response rate	2 (1.9%)	47 (58.0%)	70 (66.0%)
PASI 50 response rate	7 (6.7%)	63 (77.8%)	86 (81.1%)

n (%)

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Table 29. Overview of adverse events in subjects who inadequately responded to or were intolerant to other biologic therapies (through Week 12) (Pooled data from Studies T08 and T09)

	Overall population			Patients who inadequately responded to other biologic therapies			Patients who were intolerant to other biologic therapies		
Treatment group	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
No. of patients treated	665	664	666	104	81	106	25	21	26
Mean evaluation period (weeks)	12.0	12.2	12.2	11.9	12.2	12.2	12.3	12.2	12.1
Patients with adverse events	324 (48.7)	361 (54.4)	328 (49.2)	54 (51.9)	40 (49.4)	56 (52.8)	14 (56.0)	14 (66.7)	13 (50.0)
Patients with serious adverse events	10 (1.5)	10 (1.5)	9 (1.4)	0 (0.0)	1 (1.2)	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with adverse events leading to treatment discontinuation	13 (2.0)	2 (0.3)	10 (1.5)	4 (3.8)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious infections	3 (0.5)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (%)

PMDA considers as follows:

Although there is no objection to the applicant's view that the efficacy of ustekinumab in treating psoriatic skin lesions is as high as that of adalimumab or infliximab, the effect on joint symptoms is also important when considering the positioning of different biologics in the treatment of psoriasis and the positioning of ustekinumab needs to be further discussed, taking also account of the data on its effect in preventing the progression of joint damage, etc., which will be obtained from foreign studies. Regarding safety, as there is limited clinical experience with ustekinumab in Japan and overseas, it is necessary to collect sufficient information via post-marketing surveillance etc. and then determine the risk-benefit balance of ustekinumab and the consequent positioning of ustekinumab. Based on the novel mechanism of action of ustekinumab and foreign data, ustekinumab is expected to be useful also in patients who have responded inadequately to existing biologics. However, as no relevant Japanese data are available, it is necessary to investigate it via post-marketing surveillance etc. and provide the information to healthcare providers in clinical settings. On the other hand, the efficacy of other biologics in patients who have responded inadequately to ustekinumab has not so far been studied overseas or in Japan and such data will also be important for defining the positioning of biologics (choice between different biologics) and this is an issue for a future investigation.

4.(ii).B.(3).3) Concomitant use with conventional systemic therapy and switching from other biologics to ustekinumab

PMDA considers as follows:

Although it is envisaged that ustekinumab may be used in combination with systemic therapy such as cyclosporine and etretinate or phototherapy for refractory cases etc., there are no sufficient data regarding these combinations. Especially, when ustekinumab is used in combination with immunosuppressive systemic therapy, the possibility of developing infections or malignancies due to enhanced immunosuppression cannot be ruled out, and when ustekinumab is used in combination with phototherapy, the possibility of an increased risk of skin cancer cannot be excluded either. Thus, the package insert etc. should advise that the safety of ustekinumab in combination with other systemic therapy or phototherapy has not been established, so that the risks and benefits of such combination therapy will be determined carefully after consideration of the safety of each therapy.

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Although there is no specific evidence about the concomitant use of ustekinumab with other biologics that affect the immune system, it is desiable to avoid the use of ustekinumab in combination with other biologics, as it has been reported that the use of a combination of different biologics resulted in an increased incidence of serious infections in patients with rheumatoid arthritis. Likewise, also when switching from other biologics to ustekinumab is carried out, adequate caution should be exercised against the possible development of serious infections etc. and such precaution statement should also be included in the package insert etc.

Furthermore, it is necessary to carefully investigate, also in the post-marketing surveillance, the actual state of concomitant use with systemic therapy or phototherapy (proportion, patient background, duration of concomitant use, etc.), the safety and efficacy of the concomitant use, the actual state of switching from other biologics (proportion, patient background, washout period, etc.), and the safety and efficacy of the switching to ustekinumab, etc., and provide the obtained information to medical practice as appropriate to promote the proper use of ustekinumab.

4.(ii).B.(4) Safety

4.(ii).B.(4).1) Overview of safety

Adverse events during the placebo-controlled period through Week 12 and during the treatment period through Week 72 in Japanese Study JPN-02, and during the placebo-controlled period through Week 12 and during the entire reporting period in pooled 3 foreign psoriasis studies (T04, T08, T09) are summarized in Table 30 and Table 31, respectively.

Table 30. Adverse events in Japanese study

	Study JPN-02			
	(Through Week 12)			(Through Week 72)
	Ustekinumab		Placebo (N = 32)	Combined ustekinumab (N = 154)
	45 mg (N = 64)	90 mg (N = 62)		
Deaths	0	0	0	0
Serious adverse events	0	3 (4.8)	2 (6.3)	13 (8.4)
Serious adverse events leading to treatment discontinuation	0	3 (4.8)	1 (3.1)	6 (3.9)
Serious adverse events related to study drug	0	3 (4.8)	1 (3.1)	8 (5.2)
All adverse events	42 (65.6)	37 (59.7)	21 (65.6)	150 (97.4)
Adverse events leading to treatment discontinuation	0	4 (6.5)	2 (6.3)	6 (3.9)
Adverse events related to study drug	35 (54.7)	28 (45.2)	19 (59.4)	136 (88.3)

n (%)

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Table 31. Adverse events in pooled 3 foreign psoriasis studies

	Studies T04, T08, and T09				
	Through Week 12				Entire reporting period [a]
	Ustekinumab			Placebo (N = 732)	Combined ustekinumab (N = 2266)
	45 mg (N = 790)	90 mg (N = 792)	Combined ustekinumab (N = 1582)		
Deaths	0	1 (0.1)	1 (0.1)	0	1 (0.04)
Serious adverse events	13 (1.6)	11 (1.4)	24 (1.5)	10 (1.4)	75 (3.3)
All adverse events	455 (57.6)	409 (51.6)	864 (54.6)	369 (50.4)	1676 (74.0)
Adverse events leading to treatment discontinuation	9 (1.1)	11 (1.4)	20 (1.3)	14 (1.9)	57 (2.5)

n (%)
a: Data through Week 36 from Study T04, data through Week 52 from Study T08, and data through Week 28 from Study T09 were pooled for the table.

In Japanese Study JPN-02, there were no major differences in the incidence of adverse events during the placebo-controlled period through Week 12 among the placebo, 45 mg, and 90 mg groups and the incidence of adverse events through Week 72 was also similar between the 45 mg and 90 mg groups. The system organ class (SOC) with the highest incidence of adverse events during the placebo-controlled period in either of the ustekinumab groups was “Investigations” (18.8% [6 of 32 subjects] in the placebo group, 29.7% [19 of 64 subjects] in the 45 mg group, 22.6% [14 of 62 subjects] in the 90 mg group), followed by “Infections and infestations” (18.8% [6 of 32 subjects] in the placebo group, 20.3% [13 of 64 subjects] in the 45 mg group, 24.2% [15 of 62 subjects] in the 90 mg group) and common adverse events (≥5%) in either of the ustekinumab groups were nasopharyngitis (9.4% [3 of 32 subjects] in the placebo group, 15.6% [10 of 64 subjects] in the 45 mg group, 16.1% [10 of 62 subjects] in the 90 mg group), blood triglycerides increased (3.1% [1 of 32 subjects] in the placebo group, 10.9% [7 of 64 subjects] in the 45 mg group, 0% [0 of 62 subjects] in the 90 mg group), and eosinophil count increased (3.1% [1 of 32 subjects] in the placebo group, 4.7% [3 of 64 subjects] in the 45 mg group, 6.5% [4 of 62 subjects] in the 90 mg group). The SOC with the highest incidence of adverse events through Week 72 in the combined ustekinumab group was “Infections and infestations” (68.8% [106 of 154 subjects]). No deaths were reported. The incidences of serious adverse events during the placebo-controlled period were 6.3% (2 of 32 subjects) in the placebo group, 0% (0 of 64 subjects) in the 45 mg group, and 4.8% (3 of 62 subjects) in the 90 mg group and no consistent trend was observed and serious adverse events reported by ≥2 ustekinumab-treated subjects through Week 72 were cataract (1 subject each in the 45 mg and 90 mg groups) and fall (1 subject each in the 45 mg and 90 mg groups).

In pooled 3 foreign psoriasis studies, there were no major differences in the incidence of adverse events during the placebo-controlled period through Week 12 among the placebo, 45 mg, and 90 mg groups and the incidence of adverse events during the entire reporting period was also similar between the 45 mg and 90 mg groups and between the placebo→45 mg and placebo→90 mg groups. The SOC with the highest incidence of adverse events during the placebo-controlled period was “Infections and infestations” for all groups (22.8% [167 of 732 subjects] in the placebo group, 26.3% [208 of 790 subjects] in the 45 mg group, 24.9% [197 of 792 subjects] in the 90 mg group) and common adverse

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events (≥5%) in either of the ustekinumab groups were nasopharyngitis (7.9% [58 of 732 subjects] in the placebo group, 8.4% [66 of 790 subjects] in the 45 mg group, 8.0% [63 of 792 subjects] in the 90 mg group), headache (4.5% [33 of 732 subjects] in the placebo group, 5.7% [45 of 790 subjects] in the 45 mg group, 5.9% [47 of 792 subjects] in the 90 mg group), and upper respiratory tract infection (4.4% [32 of 732 subjects] in the placebo group, 5.7% [45 of 790 subjects] in the 45 mg group, 5.2% [41 of 792 subjects] in the 90 mg group). No major differences in the nature or incidence of adverse events were observed between the entire reporting period and the placebo-controlled period and the nature and incidence of adverse events were similar also between the two doses. Sudden cardiac death considered due to congestive cardiomyopathy occurred in 1 subject randomized to the 90 mg group in Study T09. The incidence of serious adverse events during the placebo-controlled period was similar among the treatment groups and the SOCs with the highest incidence of serious adverse events in either of the ustekinumab groups were "Cardiac disorders" (0% [0 of 732 subjects] in the placebo group, 0.1% [1 of 790 subjects] in the 45 mg group, 0.5% [4 of 792 subjects] in the 90 mg group) and "Infections and infestations" (0.4% [3 of 732 subjects] in the placebo group, 0% [0 of 790 subjects] in the 45 mg group, 0.5% [4 of 792 subjects] in the 90 mg group). There were no major differences either in the incidence of serious adverse events during the entire reporting period between the two doses and the SOCs with the highest incidence of serious adverse events in the combined ustekinumab group were "Cardiac disorders" (0.7% [15 of 2266 subjects]) and "Infections and infestations" (0.7% [15 of 2266 subjects]), which were the same as those during the placebo-controlled period.

4.(ii).B.(4).2) Significant adverse events

As shown below, the applicant explained about (a) infections, malignancy, and asthma as events theoretically associated with ustekinumab, (b) cardiovascular disorders and psoriasis as events associated with psoriasis that is the primary disease, and (c) allergy and injection site reactions as events associated with ustekinumab as an antibody preparation. PMDA's questions regarding these events and the applicant's responses are also listed below. In this section, adverse events during the entire reporting period in pooled 3 foreign psoriasis studies are based on data through Week 36 from Study T04, data through Week 52 from Study T08, and data through Week 28 from Study T09, as in the above 4.(ii).B.(4).1) Overview of safety.

4.(ii).B.(4).2).(a) Serious infections

Serious infections reported in Japanese Study JPN-02 were pneumonia in 1 subject in the 90 mg group during the placebo-controlled period and pharyngitis in 1 subject and cellulitis in 1 subject after Week 12 through 72. In pooled 3 foreign psoriasis studies, serious infections during the placebo-controlled period through Week 12 and during the entire reporting period were as shown in Table 32 and Table 33, respectively, and the event reported by ≥2 subjects in any group was cellulitis.

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Table 32. Serious infections in 3 foreign psoriasis studies (Placebo-controlled period through Week 12)

	Ustekinumab			Placebo
	45 mg	90 mg	Combined ustekinumab	
No. of subjects treated	790	792	1582	732
Mean observation period (weeks)	12.2	12.1	12.1	12.0
Mean treatment period (weeks)	4.0	4.0	4.0	4.0
No. of subjects with serious infections	0 (0.0)	4 (0.5)	4 (0.3)	3 (0.4)
Infections and infestations	0 (0.0)	4 (0.5)	4 (0.3)	3 (0.4)
Cellulitis	0 (0.0)	2 (0.3)	2 (0.1)	2 (0.3)
Herpes zoster disseminated	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)

n (%)

Table 33. Serious infections in 3 foreign psoriasis studies (Entire reporting period)

	Ustekinumab			Placebo
	45 mg	90 mg	Combined ustekinumab	
No. of subjects treated [a]	1110	1156	2266	732
Total subject-years of follow-up	725	742	1467	182
Serious infections	6	9	15	3
No. of events per 100 subject-years	0.83	1.21	1.02	1.65
95% CI [b]	(0.30,1.80)	(0.55, 2.30)	(0.57, 1.69)	(0.57,1.69)

a: Placebo-to-ustekinumab crossover subjects were included in the ustekinumab group after crossover to ustekinumab.
b: Confidence interval calculated with Fisher's exact test

In Study T08, 1 subject in the 90 mg group had herpes zoster disseminated, which was a possible opportunistic infection. Although no active tuberculosis was reported in the above Japanese and foreign studies, after the data cutoff dates of these studies, 1 case of presumed reactivation of latent tuberculosis was reported in a phase III psoriasis study (Study T25), which is ongoing in Korea and Taiwan.

According to the latest foreign post-marketing safety data collected between December 31, 2008 (International Birth Date) and August 2, 2010, a total of 37 cases of serious infections were reported and based on cumulative exposure of 18,380 patient-years estimated from the latest PSUR through June 30, 2010, its frequency was considered low. There were no reports of unconventional infections or opportunistic infections etc. and 2 cases of tuberculosis and 4 cases of sepsis were reported, but the reporting rates were low, i.e. 0.01 per 100 patient-years and 0.02 per 100 patient-years, respectively.

Based on the above, although no apparent impact of ustekinumab on infections has been seen to date, as ustekinumab is a selective immunosuppressant and may increase the risk of infections or of exacerbating infections, adequate warning and precaution information will be provided on the package insert: it will be stated in the warnings section that serious infections have been reported and that ustekinumab may increase the risk of reactivation of latent tuberculosis infection, etc. Furthermore, caution statements about infections and tuberculosis will be included in the contraindications and precautions sections as well.

PMDA asked the applicant to discuss the potential for ustekinumab to increase the risk of tuberculosis infection, taking account of its possibility of affecting the expression of TNF-α, etc. and the findings from IL-12- and IL-23-related gene knockout animals, etc.

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The applicant explained as follows:
Based on the results of pharmacodynamic assessments as part of foreign clinical studies in patients with psoriasis, a decrease in mRNA for TNF-α in lesional skin was observed after ustekinumab treatment, which is considered to be associated with recovery of inflammation (Study T01) and serum TNF-α levels were unchanged (Study T04). On the other hand, infection experiments suggested that IL-12- and IL-23-related gene knockout mice and mice treated with neutralizing antibodies to IL-12 and IL-23 had decreased host defense against pathogenic agents including mycobacteria and an increased susceptibility to initial mycobacterial infection in humans with IL-12- and IL-23-related gene deficiency has been reported [see "3.(iii) Summary of toxicology studies"]. However, based on clinical study data and foreign post-marketing safety data, the risk of tuberculosis associated with ustekinumab treatment is not high and it is just a potential risk under the current situation, which can be managed through selection of appropriate patients and the prevention and appropriate treatment of latent tuberculosis, in accordance with the above-mentioned draft package insert.

PMDA considers as follows:
Given that a few cases of tuberculosis have been reported in clinical studies and foreign post-marketing experience and that it has been suggested that IL-12- and IL-23-related gene knockout mice and genetically deficient humans have decreased host defense to mycobacteria, the risk of tuberculosis infection associated with ustekinumab cannot be denied and as proposed by the applicant, adequate warning and precaution information should be provided on the package insert etc. Moreover, it should also be noted that the incidence rate of tuberculosis is higher in Japan than in Europe and the US and the tuberculosis trend should be watched continuously.

Not only tuberculosis but also other serious infections are of greatest concern regarding the safety profile of ustekinumab. It is important to establish the procedures for cooperation between dermatologists who are the main physicians treating psoriasis and specialists who are capable of diagnosing and treating serious infections, in collaboration with the relevant academic societies, and take thorough measures to prevent and detect early adverse drug reactions, etc. [see "4.(ii).B.(5) Post-marketing safety measures"].

4.(ii).B.(4).2).(b) Malignancy
Malignancies reported in Japanese Study JPN-02 were prostate cancer in 1 subject in the 90 mg group during the placebo-controlled period and cervix carcinoma stage 0 in 1 subject after Week 12 through Week 72.

During the placebo-controlled period through Week 12 in pooled 3 foreign psoriasis studies, 2 subjects each in the placebo, 45 mg, and 90 mg groups reported malignancies and the rates of malignancies were 1.13, 0.99, and 0.98 cases per 100 subject-years of follow-up in the placebo, 45 mg, and 90 mg groups, respectively. One of the 2 subjects in the placebo group, 1 of the 2 subjects in the 45 mg group, and 2 of the 2 subjects in the 90 mg group had non-melanoma skin cancer and the rates of

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non-melanoma skin cancer were 0.57, 0.49, and 0.98 cases per 100 subject-years of follow-up in the placebo, 45 mg, and 90 mg groups, respectively. During the entire reporting period, 19 subjects in the combined ustekinumab group reported malignancies and the rate of malignancies in the combined ustekinumab group was 1.30 cases per 100 subject-years of follow-up. Of the 19 subjects, 14 subjects had non-melanoma skin cancer and the rate of non-melanoma skin cancer was 0.96 cases per 100 subject-years of follow-up. Malignancies other than non-melanoma skin cancer in the remaining 5 subjects were prostate cancer (2 subjects), breast cancer (1 subject), renal cancer (1 subject), and thyroid cancer (1 subject) and no consistent trend was observed. When the number of ustekinumab-treated subjects with malignancies other than non-melanoma skin cancer during the entire reporting period (5 cases) was compared with what would be expected in the general US population according to the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) database (7.05 cases), the standardized incidence ratio (the ratio of the observed-to-expected number of cases) and its 95% confidence interval were 0.71 [0.23,1.65] and no major differences were observed. When the rate of non-melanoma skin cancer cases per 100 subject-years of follow-up was compared between clinical studies of ustekinumab vs. other biologics, as shown in Table 34, the rate in the combined ustekinumab group was similar to those with 3 other biologics.

Table 34. Comparison of the rates of non-melanoma skin cancer with ustekinumab vs. other biologics

	Ustekinumab [a]	Infliximab [b]	Efalizumab [c]	Etanercept [d]
Total subject-years of follow-up [e]	1463	1101	1784	1062
Observed number of cases	14	17	20	12
No. of cases per 100 subject-years	0.96	1.54	1.12	1.13
95% CI [f]	(0.52, 1.61)	(0.90, 2.47)	(0.68, 1.73)	(0.58, 1.97)

a: Data from 3 foreign psoriasis studies
b: Data from foreign phase II and III clinical studies (Centocor's internal documents)
c: Unapproved in Japan. Data from The Dermatologic and Ophthalmic Drugs Advisory Committee, FDA [September 9, 2003, RAPTIVA™ (efalizumab)]
d: Unapproved for treatment of psoriasis in Japan. Enbrel (BLA 103795) data at the time of US approval.
e: Non-melanoma skin cancer includes basal cell carcinoma and squamous cell carcinoma.
f: Confidence interval calculated with Fisher's exact test

Eight cases of malignancies were collected from the latest foreign post-marketing safety data and except for prostate cancer reported by 3 patients, all malignancies were each reported by only 1 patient (anaplastic large cell lymphoma T- and null-cell types, breast cancer, gallbladder cancer, pancreatic carcinoma, renal cancer).

Based on the above, although no apparent impact of ustekinumab on malignancy has been seen to date, as ustekinumab is a selective immunosuppressant and may increase the risk of malignancy, the warning and precaution information concerning malignancy will be included in the warnings and precautions sections of the package insert, as in the case of other biologics.

PMDA considers as follows:
Although a causal relationship between ustekinumab and malignancy is not clear at present, as in the case of other biologics, the possibility that ustekinumab affects the host defense to malignant tumors cannot be denied and it is necessary to continue to conduct a large-scale, long-term investigation of the

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relationship between ustekinumab and malignancy. Generally, psoriasis patients have previously experienced phototherapy or immunosuppressants and are particularly susceptible to non-melanoma skin cancer. Therefore, it is necessary to collect post-marketing information on the occurrence of non-melanoma skin cancer in psoriasis patients and the background of patients with non-melanoma skin cancer, etc. and investigate their relationship to ustekinumab in details.

4.(ii).B.(4).2).(c) Asthma

As ustekinumab inhibits Th1 cell differentiation, it is theoretically possible that ustekinumab shifts the immune response toward a Th2 phenotype and exacerbates atopic diseases. Thus, the effects of ustekinumab on asthma were investigated.

In Japanese Study JPN-02, asthma was reported by 1 subject in the 45 mg group (1.6%) and 1 subject in the 90 mg group (1.6%), but not in the placebo group. Both events were mild in severity and both subjects with asthma had prior or concurrent bronchial asthma.

In pooled 3 foreign psoriasis studies, the incidences of asthma during the placebo-controlled period through Week 12 were 0.1% (1 of 732 subjects) in the placebo group, 0% (0 of 790 subjects) in the 45 mg group, and 0.5% (4 of 792 subjects) in the 90 mg group and the incidence during the entire reporting period in the combined ustekinumab group was 0.5% (11 of 2266 subjects). No serious adverse events related to asthma were observed in ustekinumab-treated subjects and serious asthma exacerbation occurred in 1 subject in the placebo group. There were no treatment discontinuations due to asthma. While 22.5% (450 of 1996 subjects) or 1.2% (23 of 1996 subjects) of subjects enrolled in Studies T08 and T09 had prior/concurrent seasonal allergy or atopic dermatitis, respectively (this information not collected in Study T04), the incidence of seasonal allergy during the entire reporting period in the combined ustekinumab group was 0.5% (11 of 2266 subjects) and atopic dermatitis was not reported.

Based on the above, treatment with ustekinumab is unlikely to significantly affect Th2-mediated diseases such as asthma or other atopic diseases.

PMDA considers as follows:

Although there is no objection to the applicant’s view that ustekinumab has no significant effects on Th2-mediated diseases based on the currently available information, severe asthma patients were excluded from the clinical studies and there is limited clinical experience with ustekinumab in patients with concurrent atopic dermatitis etc. Thus, it is necessary to investigate the effects of ustekinumab on these diseases in more details via post-marketing surveillance and to appropriately provide the obtained information (e.g. ustekinumab has a theoretical risk of exacerbating Th2-mediated diseases) to healthcare providers in clinical settings.

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4.(ii).B.(4).2).(d) Cardiovascular disorder

It has been reported that the risk of occlusive vascular diseases such as myocardial infarction and stroke is increased in psoriasis patients, which is considered attributable to a high prevalence, among the patients, of cardiovascular risk factors such as hypertension, hyperlipidaemia, diabetes mellitus, obesity, and smoking. Also, psoriasis itself has been reported to be a cardiovascular risk factor. Thus, as a risk to the psoriasis patient population, the impact of ustekinumab on cardiovascular adverse events was assessed.

In Japanese Study JPN-02, events classified as "cardiac disorders" or "vascular disorders" were assessed. The incidences of cardiac disorders during the placebo-controlled period were 3.1% (1 of 32 subjects, cardiac failure congestive) in the placebo group, 1.6% (1 of 64 subjects, supraventricular extrasystoles) in the 45 mg group, and 0% (0 of 62 subjects) in the 90 mg group and the incidence through Week 72 in the combined ustekinumab group was 5.8% (9 of 154 subjects, ventricular extrasystoles [5 subjects], supraventricular extrasystoles [1 subject], arrhythmia [1 subject], and left ventricular hypertrophy [1 subject], in addition to the above). The incidences of vascular disorders during the placebo-controlled period were 3.1% (1 of 32 subjects, hypertension) in the placebo group, 0% (0 of 64 subjects) in the 45 mg group, and 1.6% (1 of 62 subjects, thrombosis) in the 90 mg group and the incidence through Week 72 in the combined ustekinumab group was 5.8% (9 of 154 subjects, hypertension [7 subjects] and arteriosclerosis [1 subject], in addition to the above). The events observed in ustekinumab-treated subjects were all mild in severity.

In pooled 3 foreign psoriasis studies, the overall incidence of cardiovascular adverse events during the placebo-controlled period through Week 12 was similar for all groups, i.e. 4.5% (33 of 732 subjects) in the placebo group, 3.8% (30 of 790 subjects) in the 45 mg group, and 4.4% (35 of 792 subjects) in the 90 mg group. The overall incidences of cardiovascular adverse events during the entire reporting period were 9.2% (73 of 790 subjects) in the 45 mg group, 9.8% (78 of 792 subjects) in the 90 mg group, 6.3% (20 of 320 subjects) in the placebo→45 mg group, and 3.3% (12 of 364 subjects) in the placebo→90 mg group, and there was no increase in incidence with increasing dose.

As serious cardiovascular adverse events, objective events of "serious myocardial infarction", "serious stroke", and "cardiovascular death" were identified and assessed. As a result, 5 serious cardiovascular adverse events occurred in ustekinumab-treated subjects only during the placebo-controlled period (2 events in the 45 mg group, 3 events in the 90 mg group) and the rates were 0 events per 100 subject-years in the placebo group, 0.98 events per 100 subject-years in the 45 mg group, and 1.47 events per 100 subject-years in the 90 mg group. The rates during the entire reporting period were 0.55 events per 100 subject-years in the placebo group (since myocardial infarction [1 subject] occurred during the follow-up period after study drug discontinuation, this event was analyzed as occurring during the entire reporting period, instead of during the placebo-controlled period) and 0.61 events per 100 subject-years in the combined ustekinumab group. When "serious ischaemic events" were assessed as serious cardiovascular adverse events, the rates during the placebo-controlled period were

0 events per 100 subject-years in the placebo group, 1.48 events per 100 subject-years in the 45 mg group, and 1.47 events per 100 subject-years in the 90 mg group and the rates during the entire reporting period were 0.55 events per 100 subject-years in the placebo group and 0.95 events per 100 subject-years in the combined ustekinumab group.

Based on the above, it was considered that there was no apparent trend of increased cardiovascular risk associated with ustekinumab.

PMDA asked the applicant to explain their view on the appropriateness of the use of ustekinumab in psoriasis patients with severe cardiovascular disease.

The applicant explained as follows:
Although patients with stable cardiovascular disease were not excluded from Foreign Studies T08 and T09 and 5.6% of the subjects had myocardial infarction, coronary artery bypass, stroke, transient ischaemic attack, or atherosclerotic cardiovascular disease at baseline, as these clinical studies showed no apparent trend of increased cardiovascular risk associated with ustekinumab, there should be no problem with the use of ustekinumab even in patients with concurrent severe cardiovascular disease as long as they are appropriately managed by physicians and their symptoms are stable.

PMDA considers as follows:
Since there are no findings suggestive of increased cardiovascular risk in IL-12- and IL-23-related gene knockout animals and genetically deficient humans, at present, there is no need to restrict the use of ustekinumab in patients with cardiovascular disease including those with severe disease. However, as there is limited clinical experience with ustekinumab in these patients in the clinical studies, it is necessary to continue to carefully investigate the effects of ustekinumab on the cardiovascular system via post-marketing surveillance etc.

4.(ii).B.(4).2).(e) Psoriasis
In order to assess the effects of ustekinumab on psoriasis rebound, psoriasis-related adverse events and psoriasis rebound after stopping therapy were investigated.

In Japanese Study JPN-02, the incidences of psoriasis-related adverse events during the placebo-controlled period were 25.0% (8 of 32 subjects) in the placebo group, 1.6% (1 of 64 subjects) in the 45 mg group, and 4.8% (3 of 62 subjects) in the 90 mg group, and the incidence was lower in ustekinumab-treated subjects compared to placebo-treated subjects. The incidence through Week 72 in the combined ustekinumab group was 5.2% (8 of 154 subjects).

In pooled 3 foreign psoriasis studies, the incidences of psoriasis-related adverse events during the placebo-controlled period through Week 12 were 2.3% (17 of 732 subjects) in the placebo group, 0.4% (3 of 790 subjects) in the 45 mg group, and 1.4% (11 of 792 subjects) in the 90 mg group, and

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the incidence was lower in ustekinumab-treated subjects compared to placebo-treated subjects. The incidence during the entire reporting period in the combined ustekinumab group was 1.2% (27 of 2266 subjects).

Psoriasis rebound was evaluated in Studies T04 and T08 where evaluation was continued also after stopping ustekinumab therapy. Rebound was defined as the occurrence of new erythrodermic or pustular psoriasis or exacerbation of psoriasis to ≥125% of the baseline PASI within 3 months after the last dose of ustekinumab. In Study T04, 2 subjects had PASI ≥125% of baseline. In Study T08, the criteria for rebound were not fulfilled between the last dose and Week 40 for any subject in the treatment withdrawal group.

Based on the above, no important findings were observed regarding the effects of ustekinumab on psoriasis-related events and psoriasis rebound after stopping therapy.

As exacerbation and new onset of psoriasis have been reported with anti-TNF agents and a relevant precautionary statement is included in the package insert, PMDA asked the applicant to present the occurrence of psoriasis in non-psoriasis clinical studies of ustekinumab and then explain whether a similar precautionary statement is necessary also for ustekinumab.

The applicant explained as follows:
In addition to psoriasis clinical studies, multiple sclerosis and Crohn's disease clinical studies were conducted overseas and a total of 336 subjects received ustekinumab. In these clinical studies, serious psoriasis was not reported and non-serious psoriasis was reported by 1 patient with Crohn's disease, but the patient had a history of psoriasis and its causal relationship to ustekinumab was denied. As described above, Japanese and foreign clinical studies showed no relationship between ustekinumab and exacerbation or new onset of psoriasis and although the mechanism of exacerbation or new onset of psoriasis induced by anti-TNF agents has not been elucidated at molecular level, the molecular target of ustekinumab is different from that of anti-TNF agents. Therefore, this risk may be lower with ustekinumab compared with anti-TNF agents and a precautionary statement in the package insert etc. should be unnecessary at present.

PMDA accepts the applicant's response at present, but considers that it is necessary to collect further information on the effects of ustekinumab in patients with other diseases, etc. and continue to investigate the risk associated with ustekinumab because the clinical studies of ustekinumab were conducted primarily in psoriasis patients and it is difficult to appropriately assess exacerbation or new onset of psoriasis in psoriasis patients.

4.(ii).B.(4).2).(f) Injection site reactions and allergic reactions
In Japanese Study JPN-02, the incidences of injection site reactions were 0.6% (1 of 158 subjects) following administration of placebo and 1.9% (3 of 154 subjects) following administration of

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ustekinumab and these events were all mild in severity. While no cases of anaphylactic reactions or serum sickness reactions were reported, as adverse events of suspected allergic reactions, eczema (7.1% [11 of 154 subjects]), urticaria (3.9% [6 of 154 subjects]), pruritus (1.9% [3 of 154 subjects]), injection site urticaria (0.6% [1 of 154 subjects]), rash (0.6% [1 of 154 subjects]), and pruritus generalised (0.6% [1 of 154 subjects]) were observed. The incidence of anti-ustekinumab antibody development in the combined ustekinumab group was 6.5% and none of the antibody-positive subjects had an adverse event of suspected anaphylactic reaction and the 3 subjects with injection site reactions were not antibody-positive.

In pooled 3 foreign psoriasis studies, the incidences of injection site reactions were 2.6% (60 of 2304 subjects) following administration of placebo and 3.1% (71 of 2266 subjects) following administration of ustekinumab and no major differences were observed. Although no adverse events of suspected anaphylactic reactions or serum sickness-like reactions were observed, as adverse events of suspected allergic reactions, rash and urticaria were reported and the incidence was <1% for both events. The incidence of anti-ustekinumab antibody development in the combined ustekinumab group was 3.7% and none of the antibody-positive subjects had an adverse event of suspected anaphylactic reaction. In foreign phase III studies (Studies T08 and T09), the incidences of injection site reactions were 7.0% (5 of 71 subjects) in antibody-positive subjects and 3.8% (71 of 1870 subjects) in antibody-negative subjects, which indicated that there is no relationship between anti-ustekinumab antibody development and injection site reactions.

Based on the latest foreign post-marketing safety data, 1 case of anaphylactic reaction and 4 cases of hypersensitivity were collected and as it was considered that serious allergic reactions should be recognized as a risk associated with ustekinumab, it will be stated, as precaution information, in the adverse reactions section of the package insert that serious allergic reactions such as possible anaphylactic events and angioedema may occur.

PMDA considers as follows:
The precaution information concerning serious allergic reactions associated with ustekinumab is appropriate at present. Meanwhile, as it seems that the occurrence of serious allergic reactions tends to increase in the foreign post-marketing experience compared to in the clinical studies, it is necessary to continue to watch the trend of occurrence and review the precaution information as appropriate. During treatment with ustekinumab, it is important to be prepared so that drug therapy and emergency measures can be used promptly in response to anaphylaxis etc. and then to closely monitor the patient’s condition.

In addition, the occurrence of autoimmune disease, demyelinating disease, interstitial pneumonia, blood disorder, and hepatic disorder etc., which are considered to be important adverse reactions to anti-TNF agents (similar drugs), was also investigated based on the clinical study data and the latest foreign post-marketing safety data etc., which has suggested no risk of these adverse events associated

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with ustekinumab at present. Thus, no particular precaution information etc. are necessary. However, given that the clinical experience with ustekinumab is very limited compared to the experience with anti-TNF agents, that the mechanism of these adverse events associated with anti-TNF agents is not elucidated, and that anti-TNF agents and ustekinumab are both antibody products affecting the immune system, etc., the possibility that ustekinumab also causes similar adverse reactions cannot be denied. Therefore, it is necessary to carefully investigate the occurrence of these events also via post-marketing surveillance.

4.(ii).B.(5) Post-marketing safety measures

PMDA considers as follows:

Since the possibility that ustekinumab causes adverse reactions such as serious infections and malignancy cannot be denied and the long-term safety of ustekinumab is unknown in many aspects, as in the case of existing biologics, a large-scale drug use-results survey with the physicians and all the patients registered and a long-term special drug use-results survey to appropriately follow the patients for the development of malignancy, etc., should be conducted. In order to promote proper use of ustekinumab, information should be provided to healthcare providers and patients appropriately and promptly by giving detailed materials to healthcare providers such as physicians, developing a patient's guide etc., which describe the risks and benefits of ustekinumab in an appropriate and easy-to-understand manner, and collecting and disclosing post-marketing information accordingly via the Internet, etc.

Furthermore, dermatologists are the main physicians to treat psoriasis, and it is essential for them, prior to the use of ustekinumab, to establish cooperation with internists, etc., who are capable of handling serious adverse drug reactions such as infections, in terms of safety measures. Thus, PMDA asked the applicant to explain in details about the requirements for medical institutions to use ustekinumab and the specific way of cooperation with internists, etc.

The applicant explained as follows:

The requirements for medical institutions to use ustekinumab are as follows: Ustekinumab can be used under the management/supervision/guidance of specialist(s) who are familiar with the diagnosis and treatment of psoriasis and who know the risks of ustekinumab very well; and tuberculosis screening can be performed and adverse drug reactions including serious infections can be diagnosed and treated at the medical institution or in its affiliated medical institution. The requirements for affiliated medical institutions are as follows: tuberculosis screening can be performed and adverse drug reactions including serious infections can be diagnosed and treated in cooperation with the prescribing medical institution (except for general hospitals having relevant cooperating departments). Moreover, the procedures for cooperation between the medical institutions have been planned as follows: (a) Affiliated medical institutions and cooperating physicians there will be identified through contacts with physicians using ustekinumab and not only prescribing physicians but also cooperating physicians will be explained about the safety profile of ustekinumab and actions to be taken in the

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event of adverse drug reactions and the importance of determining whether or not to use ustekinumab, etc., (b) prescribing physicians will be requested to instruct their patients to contact them promptly if any abnormality occurs after administration of ustekinumab and to refer their patients to the affiliated medical institutions promptly if adverse drug reactions such as infections are suspected, and (c) portable patient cards for the patients to visit the affiliated medical institutions with and forms (patient diaries, etc.) that can be shared between the prescribing physicians and the affiliated medical institutions and that are used by patients themselves to record their health status will be prepared, etc.

As cooperation from the relevant academic societies, etc., is also considered essential for promoting proper use of ustekinumab and implementing safety measures, the Japanese Dermatological Association will be requested to take the initiative in developing a guideline for the use of ustekinumab.

PMDA considers as follows:
The applicant's response is largely acceptable, but it is important to confirm that cooperation with other departments/other medical institutions is ensured, via post-marketing surveillance.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the documents appended to the new drug application (5.3.3.2.1, 5.3.5.1.2-1). As a result, enrollment of subjects who met the exclusion criteria of the protocol and flaws in the contract for the partial transfer of trial-related duties were found at some trial sites, but PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of ustekinumab in the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy has been demonstrated and its safety is acceptable in view of its observed benefits. Since ustekinumab is a

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biologic with a novel mechanism of action and offers a new therapeutic option, it has clinical significance. The INDICATION statement and the DOSAGE AND ADMINISTRATION statement need to be further discussed. Regarding safety, serious adverse drug reactions such as infections may occur following administration of ustekinumab. Therefore, prior to the use of ustekinumab, the patient's symptoms, etc. should be monitored closely and the risks and benefits of ustekinumab should be weighed. A post-marketing drug use-results survey, which covers all the patients treated with ustekinumab, should be conducted to further investigate the safety of ustekinumab in psoriasis patients.

The application may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

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Review Report (2)

November 10, 2010

I. Product Submitted for Registration

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010

II. Content of the Review

The outlines of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Indications

PMDA concluded that ustekinumab should be indicated only for the patients who have had an inadequate response or intolerance to phototherapy or conventional systemic therapy, which was supported by the expert advisors. PMDA considered that the INDICATION statement should be modified to include the following statements in the Precautions for Indications section of the package insert: ustekinumab should be used in (a) patients who have a body surface area involvement of ≥10% and who have had an inadequate response to conventional systemic therapy including UV-light therapy (excluding biologics) or (b) patients with refractory skin lesion or joint inflammation. PMDA requested the applicant to modify the indications and the applicant accepted it.

[Indications]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris and psoriatic arthritis

In addition, PMDA instructed the applicant to include in the package the statement to the effect that ustekinumab should only be used by physicians who are familiar with the treatment of psoriasis, etc. to ensure correct diagnosis, selection of eligible patients, and the proper use of ustekinumab, and that ustekinumab should be used in cooperation with internists, etc., who are capable of handling adverse reactions to ustekinumab. The applicant responded that in order to give adequate warning, it will be stated in the WARNING section of the package insert that ustekinumab should be used by physicians

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with experience in treating psoriasis in cooperation with physicians with adequate knowledge about ustekinumab.

(2) Dosage and administration

PMDA has concluded that a dose increase should be recommended as follows: "If the effect is insufficient, a dose of 90 mg may be used", which was supported by the expert advisors. PMDA considered that the DOSAGE AND ADMINISTRATION statement should be modified as shown below and that it should be stated in the Precautions of Dosage and Administration section that treatment with ustekinumab should not be continued without careful consideration if the patient does not respond to an increased dose of ustekinumab. PMDA requested the applicant to take actions accordingly and the applicant accepted it.

[Dosage and administration]
The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter.
If the effect is insufficient, a dose of 90 mg may be used.

Since ustekinumab is administered every 12 weeks after Week 4, it is not a heavy burden for most patients to receive injections at the medical institution. Therefore, patient self-administration has not been proposed.

(3) Post-marketing surveillance etc.

PMDA has concluded as follows

Ustekinumab may cause adverse reactions including serious infections. When ustekinumab is indicated for treatment of psoriasis, it is necessary to ensure the patient's safety with close cooperation between dermatologists and internists etc. Thus, after the market launch, a drug use-results survey, which covers all the patients treated with ustekinumab, should be conducted until data from a certain number of patient will be accumulated, in order to obtain safety information on ustekinumab in psoriasis patients as soon as possible and confirm the effectiveness of safety measures taken in cooperation with other departments/other medical institutions. Furthermore, a long-term, specified drug use-results survey to monitor the development of infections and malignancy should be conducted. On the basis of the above conclusion, PMDA requested the applicant to take actions accordingly.

The applicant responded as follows:

A long-term, specified drug use-results survey with an observation period of 52 weeks, which covers all the patients treated with ustekinumab, will be conducted. For this survey, (a) the priority items will be allergy, cardiac disorder, autoimmune disease, pancytopenia, interstitial pneumonia, demyelinating disease, and hepatic disorder, etc., which have been reported with anti-TNF agents, as well as infections, tuberculosis, and malignancy, (b) the following information will be collected: the efficacy and safety of an increased dose of ustekinumab, the safety of switching from other biologics to

ustekinumab, the actual state of concomitant use with phototherapy or other systemic therapies, the effects of ustekinumab on atopic diseases such as asthma and the cardiovascular system, etc., the efficacy of ustekinumab in patients with diabetes co-morbidity, and disease activity as measured by DAS 28 in patients with psoriatic arthritis, etc. and (c) analyses will be performed when the information from 1500 patients have been collected, but the survey will be continued until the regulatory authority's final evaluation is obtained. Patients will be followed for the development of serious infections and malignancy for up to 3 years.

PMDA considers that the survey should be conducted promptly and the obtained results should be provided to clinical practice appropriately.

III. Overall Evaluation

As a result of the above review, PMDA concludes that ustekinumab may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indications]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris and psoriatic arthritis

[Dosage and administration]
The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) is administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter.
If the effect is insufficient, a dose of 90 mg may be used.

[Conditions for approval]
The applicant is required to:
(1) Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of Ustekinumab.
(2) Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the long-term safety of the product and the occurrence of infections etc.

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https://web.archive.org/web/20170712033550/https://www.pmda.go.jp/files/000153747.pdf

Report on the Deliberation Results

December 6, 2010

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name]	Ustekinumab (Genetical Recombination) (JAN*)
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	January 21, 2010

[Results of deliberation]
In the meeting held on November 29, 2010, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs.

The conditions for approval should be modified as follows.

After modification
[Conditions for approval]
The applicant is required to:
1. Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.
2. Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the efficacy and long-term safety of the product, including the occurrence of infections, etc.

Before modification
[Conditions for approval]
The applicant is required to:
1. Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.
2. Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the efficacy and long-term safety of the product and the occurrence of infections etc.

(The underlined parts are the changes.)

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version

Japanese Accepted Name (modified INN)

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version

Review Report

November 10, 2010
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010
[Dosage form/Strength] A solution for injection in a prefilled syringe. Each prefilled syringe (0.5 mL) contains 45 mg of Ustekinumab (Genetical Recombination).
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure] See Figure 1 and Figure 2 below.
Molecular formula: H-chain $C_{2207}H_{3410}N_{582}O_{671}S_{17}$
L-chain $C_{1034}H_{1596}N_{274}O_{337}S_{6}$
Molecular weight: 148,079 to 149,690
Chemical name:

Ustekinumab is a recombinant human IgG1 monoclonal antibody against the p40 subunit of human interleukin-12 and interleukin-23.
Ustekinumab is produced in mouse myeloma (Sp2/0) cells.
Ustekinumab is a glycoprotein (molecular weight, 148,079-149,690) composed of 2 H-chain (γ1-chain) molecules consisting of 449 amino acid residues each and 2 L-chain (κ-chain) molecules consisting of 214 amino acid residues each.

[Items warranting special mention] None
[Reviewing office] Office of New Drug IV

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version

Heavy Chain

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY   60
                          22-96
SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR PGQGYFDFWG QGTLVTVSSS  120

STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG  180
                     146-202
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP  240
                                   222 LC  228 HC  231 HC  N-Glycan
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS  300
                          263-323
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL  360

TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ  420
  369-427
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK                                    449
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Light Chain

```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS   60
                          23-88
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ GTKLEIKRTV AAPSVFIFPP  120

SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
                134-194
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214
                                    HC
```

Figure 1. Heavy and light chains of ustekinumab

Amino acid sequences of the heavy and light chains of ustekinumab are indicated in the single-letter code.
Complementarity-determining regions are underlined.
H-chain K449: partial processing

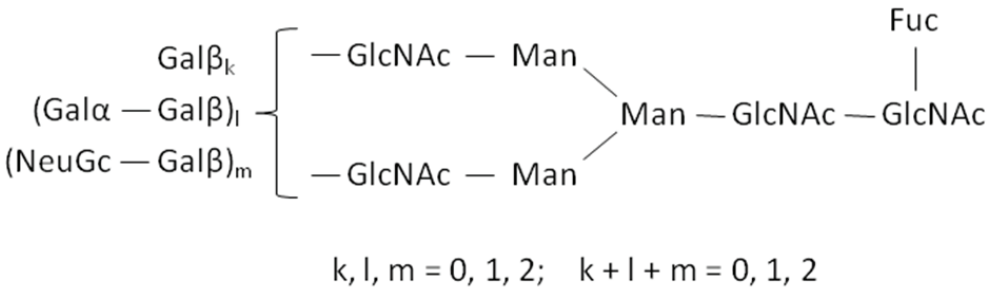


Figure 2. Carbohydrate structure

Review Results

November 10, 2010

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010

[Results of review]
Based on the submitted data, the efficacy of the product in the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy has been demonstrated and its safety is acceptable in view of its observed benefits.

Serious adverse drug reactions such as infections may occur following administration of the product. Therefore, prior to the use of the product, the patient's symptoms etc. should be monitored closely and the risks and benefits of the product should be weighed carefully. The risks of the product should be fully explained to the patient as well. It is necessary to closely monitor the course of the disease also after the initiation of treatment. After the market launch, a post-marketing surveillance study focusing on the occurrence of serious infections etc., covering all the patients treated with the product, and a long-term survey to follow the patients for the development of infections and malignancy etc. need to be conducted.

As a result of its review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

[Indication]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris and psoriatic arthritis

[Dosage and administration]
The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter. If the effect is insufficient, a dose of 90 mg may be used.

[Conditions for approval]
The applicant is required to:
(1) Conduct a post-marketing drug use-results survey, which covers all the patients treated with the

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product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of the product.

(2) Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the long-term safety of the product and the occurrence of infections etc.

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Review Report (1)

October 12, 2010

I. Product Submitted for Registration

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010
[Dosage form/Strength] A solution for injection in a prefilled syringe. Each prefilled syringe (0.5 mL) contains 45 mg of Ustekinumab (Genetical Recombination).

[Proposed indication]

Moderate to severe psoriasis vulgaris

Psoriatic arthritis with moderate to severe plaque psoriasis

[Proposed dosage and administration]

The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter.

A dose of 90 mg may be administered in patients weighing >100 kg.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

The active substance Ustekinumab (Genetical Recombination) (ustekinumab) is a human immunoglobulin G (IgG) 1κ monoclonal antibody (mAb) against human interleukin (IL)-12/23 p40, developed by Centocor Inc. (the US) (currently Centocor Ortho Biotech Inc.).

Psoriasis vulgaris is an immune-mediated inflammatory keratosis with alternating periods of remissions and flare-ups, characterized by the formation of infiltrative erythematous plaques or irregularly shaped erythematous plaques. Psoriatic arthritis is a rheumatoid factor-negative inflammatory arthritis associated with psoriasis of skin. In general, for patients with mild (body surface area [BSA] involvement of ≤10%) to moderate (BSA involvement of 10%-30%) disease, topical corticosteroids, topical vitamin D_3 derivatives, and combination therapy of these agents are used. For patients with moderate to severe disease, phototherapy and systemic therapies (e.g., cyclosporine, and etretinate) are used. Anti-TNF-α agents, infliximab and adalimumab, were approved in January 2010 to treat patients who have had an inadequate response to these conventional therapies.

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T cells are believed to be fundamental to the development of the disease and to play a central role in the pathology of the disease. Ustekinumab has a novel mechanism of action of inhibiting the function of T cells by binding with high affinity to IL-12/23 p40, the shared subunit of human IL-12 and IL-23 that are involved in T cell differentiation. Thus, ustekinumab was developed as a therapeutic drug for psoriasis.

The clinical development of ustekinumab for the treatment of psoriasis began in 20[redacted] overseas and ustekinumab was first approved in Canada in December 2008 for the indication of "moderate to severe plaque psoriasis." As of September 2010, ustekinumab has been approved in 52 countries for indications related to psoriasis.

In Japan, the clinical development of ustekinumab for the treatment of psoriasis began in [redacted] 20[redacted]. Based on the claim that Japanese clinical studies etc. have confirmed the efficacy and safety of ustekinumab, the applicant has filed a marketing application for ustekinumab.

2. Data relating to quality

2.A Summary of the submitted data

Ustekinumab is produced in murine myeloma (Sp2/0) cells, and it is a glycoprotein (molecular weight, 148,079-149,690) composed of two heavy chain (γ1chain, $C_{2207}H_{3410}N_{582}O_{671}S_{17}$; molecular weight, 49,377.29) molecules consisting of 449 amino acid residues each and two light chain (κ-chain, $C_{1034}H_{1596}N_{274}O_{337}S_6$; molecular weight, 23,449.76) molecules consisting of 214 amino acid residues each. Ustekinumab contains a single *N*-linked glycosylation site (Asn299) in the constant region of each heavy chain. The molecule contains a total of 16 disulfide bonds.

2.A.(1) Drug substance manufacturing process

2.A.(1).1) Assembly of the gene expression construct and cell banking

[redacted]

A genomic library of the cell line A was prepared to clone human anti-IL-12 IgG1 heavy and light chain genes. [redacted]. A master cell bank (MCB) was prepared from the cell line D and a working cell bank (WCB) was

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prepared from the MCB. Although bovine serum was used in the process before the selection of the cell line D, no raw materials of animal origin were used thereafter.

2.A.(1).2) Characterization and control of cell banks

MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) were characterized as shown in Table 1.

Table 1. Results of characterization of cell banks etc.

Test	Test results			
	MCB	WCB		CAL
	Lot: a	Lot: b	Lot: c	Lot: d
Isoenzyme analysis	Of mouse origin	Of mouse origin	Of mouse origin	Of mouse origin
Double immunodiffusion	NT	[redacted]		NT
cDNA sequence	cDNA sequence/deduced amino acid sequence agreed with the reference sequence.	NT	NT	Consistent with MCB
Analysis of patterns of DNA inserts	Consistent with the banding patterns of the heavy and light chain vectors	NT	NT	Consistent with MCB
Gene copy number	[redacted]	NT	NT	[redacted]
[redacted]	NT	NT	NT	[redacted]

NT: Not tested

Purity tests as shown in Table 2 were performed and no viral or non-viral infectious agents were detected other than ecotropic recombinant virus (ERV) and A-type and C-type retrovirus-like particles in the MCB, WCB, and CAL, within the scope of the tests performed.

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Table 2. Results of tests for purity of cell banks etc.

Test			Acceptance criteria	Test results			
				MCB	WCB		CAL
				Lot: a	Lot: b	Lot: c	Lot: d
Sterility			Negative	Negative	Negative	Negative	NT
Mycoplasma testing (culture method and non-cultural method)			Negative	Negative	Negative	Negative	NT
Tests for retroviruses and other endogenous viruses	Infectivity assays	Assay for ERV[a)]	Report results only	Negative	Negative	Negative	NT
		S^+L^- focus assay[b)]	Report results only	Negative	Negative	Negative	NT
		XC plaque assay[c)]	Report results only	Negative	Negative	Negative	NT
		Co-cultivation assay for ERV[a)]	Report results only	ERV detected	ERV detected	ERV detected	ERV detected
		Mink cell focus assay[c)]	Report results only	Negative	Negative	Negative	Negative
	Electron microscopy		Report results only	A-type and C-type retrovirus-like particles observed	A-type and C-type retrovirus-like particles observed	A-type and C-type retrovirus-like particles observed	A-type and C-type retrovirus-like particles observed
	Reverse transcriptase		Report results only	Reverse transcriptase detected	Reverse transcriptase detected	Reverse transcriptase detected	Reverse transcriptase detected
Tests for non-endogenous or adventitious viruses	*In vitro* assays	Assay for adventitious viruses[d)]	Negative	Negative	Negative	Negative	Negative
		Bovine virus assay[e)]	Negative	Negative	Negative	Negative	Negative
		Assay for adventitious bovine viruses derived from components other than bovine serum[f)]	Negative	Negative	NT	NT	Negative
	In vivo assays	Assay to reveal latent viruses[g)]	Negative	Negative	Negative	Negative	Negative
		Assay for mouse thymic virus	Negative	Negative	Negative	Negative	Negative
	Mouse antibody production test[h)]		Negative	Negative	Negative	Negative	Negative

NT: Not tested

[a)] *Mus dunni* cells were used.

[b)] $MiCl_1$ S^+L^- cells and Mv1Lu mink cells were used.

[c)] SC-1 cells were used.

[d)] MRC-5 cells, Vero cells, HeLa cells, Sp2/0 cells (MCB and WCB), and [redacted] indicator cell line (MCB and CAL) were used.

[e)] Bovine turbinate cells were used and immunostained for bovine adenovirus type 5, bovine parvovirus, bovine viral diarrhea virus, infectious bovine rhinotracheitis virus, and bovine parainfluenza virus type 3.

[f)] Bovine turbinate cells and Vero cells were used.

[g)] Inoculated into adult mice, suckling mice, and guinea pigs, and embryonated eggs.

[h)] polyoma virus, Sendai virus, lymphocytic choriomeningitis virus, ectromelia virus, reovirus type 3, K virus, minute virus of mice, pneumonia virus of mice, mouse hepatitis virus, mouse encephalomyelitis virus, mouse cytomegalovirus, mouse rotavirus, lactic dehydrogenase virus, Hantaan virus, mouse thymic virus, and mouse adenovirus were used. For Lot c of WCB and CAL, mouse parvovirus was also used.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. The MCB is stored at more than one site.

[redacted]

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[redacted]. A new WCB will be generated periodically.

2.A.(1).3) Manufacturing process

The manufacturing process for the drug substance is as shown below.

	Manufacturing process	In-process controls
Stage 1	**Preculture and Expansion** Thawing of WCB [redacted] Equipment: culture flasks, culture bags, and [redacted]-L bioreactor	
Stage 2	**Production Culture** [redacted] Equipment: [redacted]-L production bioreactor	bioburden, mycoplasma, and *in vitro* assay for adventitious viruses
Stage 3	[redacted]	[redacted]
Stage 4	**Thawing and pooling of [redacted] eluate**	
Stage 5	**Solvent/Detergent (S/D) Treatment** [redacted]	[redacted]
Stage 6	**Cation Exchange Chromatography** Carrier: [redacted]	bioburden and endotoxin
Stage 7	**Anion Exchange Chromatography** Carrier: [redacted]	bioburden and endotoxin
Stage 8	**Virus Removal Filtration** Filter: [redacted]	protein concentration, bioburden, and endotoxin
Stage 9	[redacted]	[redacted]
Stage 10	**Preparation of ustekinumab formulated bulk (FB)** [redacted] **Ustekinumab FB**	[redacted]

Note: Critical steps are enclosed in boxes.

[redacted]. The cause of the contamination with *Staphylococcus epidermidis* was identified and then measures were taken to prevent the recurrence.

Table 3. Attributes evaluated in process validation for each stage

Stages	Attributes evaluated
Stage 1	[redacted]
Stage 2	bioburden, *in vitro* assay for adventitious viruses, and mycoplasma testing (culture method and non-cultural method)
Stage 3	[redacted]
Stage 4	bioburden and endotoxin
Stage 5	[redacted]
Stage 6	[redacted]
Stage 7	[redacted]
Stage 8	[redacted]
Stage 9	[redacted]
Stage 10	[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

Furthermore, based on the stability evaluation of intermediates produced during the manufacturing process, the storage conditions and storage periods were determined.

2.A.(1).4) Adventitious agents safety evaluation

In the manufacturing process for the drug substance, no raw materials of animal origin were used other than Sp2/0 host cells.

Purity tests were performed on the MCB, WCB, and CAL and no viral or non-viral infectious agents were detected other than ERV, and A-type and C-type retrovirus-like particles [see "2.A.(1).2) Characterization and control of cell banks"]. [redacted] batches of culture fluid were evaluated for the presence of retrovirus (assay for ERV[1], S^+L^- focus assay[1], XC plaque assay[1], mink cell focus assay[1], electron microscopy[2]) in process validation and no retrovirus or adventitious virus was detected other

[1] Samples taken from bioreactor on around Day [redacted] or [redacted] of cell culture for productionwere evaluated.

[2] Samples taken from bioreactor on around Days [redacted], [redacted], and [redacted] of cell culture for productionwere evaluated. Note that samples on Day [redacted] instead of samples taken from bioreactor on around Day [redacted] were used for [redacted] of [redacted] batches were evaluated.

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than ERV and retrovirus-like particles. In-process testing is performed to ensure that the culture fluid at the end of the production run is free of mycoplasma and adventitious virus contamination.

In order to evaluate the capacity of the purification process to clear viruses, viral clearance studies were performed with relevant viruses and non-specific model viruses as shown in Table 4, which demonstrated that all viruses are adequately removed by the purification process. It has been discussed that the overall reduction factor for ERV indicates that the purification process provides adequate endogenous retrovirus clearance.

Table 4. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10}) (One-sided 95% confidence interval [CI] in parenthesis)			
	ERV	Poliovirus type 1	Reovirus type 3	Pseudorabies virus
Stage 3: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 5: S/D treatment	[redacted]	NT	NT	[redacted]
Stage 7: Anion exchange chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Stage 8: Viral removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>19.4 (1.0)	≥6.6 (0.7)	≥10.5 (0.9)	≥14.6 (0.8)

NT: Not tested

2.A.(1).5) Manufacturing process development (Comparability)

During the development of ustekinumab, changes were made to the manufacturing process in order to establish a robust manufacturing process for supplying a sufficient quantity of the drug product at an appropriate manufacturing-scale. The major changes are shown in Table 5.

Table 5. Major changes made to the manufacturing process

Manufacturing method	Manufacturing method A	Manufacturing method B	Manufacturing method C	Manufacturing method D
Intended use	Non-clinical studies, Foreign phase I clinical studies	Foreign phase II clinical studies: Psoriasis	Foreign phase II clinical studies: Psoriatic arthritis Multiple sclerosis	Foreign phase III clinical studies Japanese Study JPN-01 Japanese Study JPN-02 To-be-marketed drug product
Cell line[a]	B	Same as left	D	Same as left
[redacted]	Medium containing bovine-derived raw materials	Same as left	[redacted]	Same as left
[redacted]	[redacted]L	[redacted]L	[redacted]L	[redacted]L
[redacted]	[redacted]	[redacted]	Same as left	Same as left
[redacted]	[redacted]	[redacted]	[redacted]	Same as left
Virus removal membrane	[redacted] virus retentive filter	[redacted] virus retentive filter	Same as left	Same as left
[redacted]	Of animal origin	Same as left	Of plant origin	Same as left
Dosage form	Lyophilized	Same as left	Same as left	Liquid

a: The cell line B and the cell line D are derived from the same murine myeloma cell line.

[redacted]. The following tests for the comparability exercise were conducted, which demonstrated comparability between the drug substances produced by Manufacturing Methods A and B.

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SDS-PAGE, size exclusion chromatography (SE-HPLC), charge heterogeneity (isoelectric focusing [IEF], ion exchange chromatography [IE-HPLC]), potency (a cell-based assay), and process-related impurities (bioburden, endotoxin, residual Protein A, bovine IgG)

For Manufacturing Method C, the cell line and medium etc. were changed. The following tests for the comparability exercise of the drug substances/drug products produced by Manufacturing Methods A and C were conducted.

Peptide mapping, N-terminal amino acid sequencing, circular dichroism spectra (far-ultraviolet, near-ultraviolet), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS), electrospray ionization mass spectrometry (ESI-MS), oligosaccharide mapping, SDS-PAGE, SE-HPLC, charge heterogeneity (IEF, IE-HPLC), potency (a cell-based assay), process-related impurities (HCP, host cell DNA, residual Protein A), degradation profile and degradation rate

[redacted]. Other test results were similar. In addition, a non-clinical study in cynomolgus monkeys showed no differences in pharmacokinetic parameters between products manufactured by method A and C [see "3.(ii) Summary of pharmacokinetic studies"]. These results demonstrated comparability between pre-change and post-change drug substances/drug products.

[redacted].The following tests for the comparability exercise were conducted, which demonstrated comparability between the drug products produced by Manufacturing Methods C and D.

Peptide mapping, N-terminal amino acid sequencing, circular dichroism spectra (far-ultraviolet, near-ultraviolet), differential scanning calorimetry, sedimentation coefficient, ESI-MS, oligosaccharide mapping, SDS-PAGE, SE-HPLC, charge heterogeneity (IEF, IE-HPLC), potency (a cell-based assay), degradation profile and degradation rate, product-related impurities (aggregates, truncated forms), and process-related impurities (HCP, host cell DNA, residual Protein A)

2.A.(2) Drug substance

2.A.(2).1) Structure and composition

The drug substance has been characterized as follows.

2.A.(2).1).(a) Primary structure

● The amino acid sequence of ustekinumab, as determined by N-terminal amino acid sequencing by Edman degradation and peptide mapping, agreed with the one deduced from cDNA.

● Heterogeneity in C-terminal Lys residues of the heavy chain, which is commonly observed in IgG1,

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was detected by LC/electrospray ionization quadrupole time-of-flight mass spectrometry (ESI-QTOF MS).

2.A.(2).1).(b) Higher order structure

● Two intra-chain disulfide bonds in each light chain, four intra-chain disulfide bonds in each heavy chain, and four inter-chain disulfide bonds (two inter-heavy chain disulfide bonds in the hinge region, one inter-heavy-light chain disulfide bond for each heavy and light chain pair) were identified by peptide mapping under non-reducing conditions. Free sulfhydryl analysis using Ellman's reagent revealed that [redacted]% of all Cys residues are present as free sulfhydryl groups, confirming that almost all Cys residues are involved in disulfide bond formation, as is the case with a typical IgG1.

● [redacted].

● [redacted]

● The sedimentation coefficient as determined by sedimentation velocity analytical ultracentrifugation (SV-AUC) was typical of IgG.

● The apparent molecular weight of ustekinumab, as measured by sedimentation equilibrium AUC, was approximately [redacted], which was close to the molecular weights of different glycoforms of ustekinumab, approximately 148,000 to 150,000, as measured by mass spectrometry, indicating that the molecule is monomeric in solution.

● Differential scanning calorimetry analysis showed that ustekinumab has a folded structure, with a thermally stable conformation.

2.A.(2).1).(c) Carbohydrate structure

● Fragment analysis by peptide mapping showed that ustekinumab is glycosylated at Asn299 of the heavy chain.

● Analysis of neutral monosaccharide composition indicated that ustekinumab has a biantennary, core-fucosylated *N*-glycan with galactose heterogeneity. No galactosamine was detected, indicating the absence of *O*-linked glycosylation.

● Oligosaccharide mapping and sequential exoglycosidase digestion revealed that ustekinumab has [redacted] types of biantennary, core-fucosylated glycans with galactose and sialic acid heterogeneity. Neutral oligosaccharides (G0F, [redacted]%; G1F, [redacted]%; G2F, [redacted]%) and sialylated oligosaccharides accounted for [redacted]% and [redacted]%, respectively, of the total glycans.

● The results of sialic acid analysis revealed that [redacted]% of the total sialic acid was *N*-glycolylneuraminic acid (NGNA) and [redacted]% was *N*-acetylneuraminic acid (NANA).

2.A.(2).1).(d) Isoforms

● The mass spectrum showed multiple peaks due to the heterogeneity among multiple *N*-glycan structures and partial removal of heavy chain C-terminal Lys. After removing the heavy chain C-terminal Lys residues, the mass spectrum revealed only peaks derived from different *N*-glycans.

● After removing the heavy chain C-terminal Lys residues, both IEF and cIEF profiles revealed [redacted] isoforms in the pI range of [redacted] to [redacted]. Further analyses by IE-HPLC and peptide mapping revealed isoforms with oligosaccharides containing [redacted] to [redacted] sialic acids and those with neutral oligosaccharides.

● The mass spectra of blood samples from the patients treated with ustekinumab produced by the cell line B revealed [redacted] major isoforms. The clearance profiles of these isoforms in the serum over time were similar.

2.A.(2).1).(e) Other physicochemical properties

● The extinction coefficient was [redacted] $(mg/mL)^{-1}cm^{-1}$.

2.A.(2).1).(f) Biological properties

● Enzyme immunoassay (EIA) and surface plasmon resonance etc. showed that ustekinumab binds specifically to human IL-12 and human IL-23.

● The equilibrium constants for ustekinumab binding to human IL-12 and human IL-23 were [redacted] pmol/L and [redacted] pmol/L, respectively.

● Ustekinumab inhibited human IL-12 and human IL-23 from binding to their receptors (human IL-12Rβ1, human IL-12Rβ1/β2 receptor complex, human IL-12Rβ1/23R receptor complex) by binding to human IL-12/23p40. Ustekinumab could not bind to human IL-12 or human IL-23 that was already bound to their receptors, resulting in no induction of complement dependent cytotoxicity (CDC) [see "3.(i) Summary of pharmacology studies"].

● In an *in vitro* assay using human H cells, ustekinumab was shown to inhibit human IL-12-induced IFN-γ production. In [redacted]-month stability studies at 5°C, [redacted]°C, and [redacted]°C, the activity of ustekinumab decreased over time when stored at [redacted]°C and [redacted]°C, showing that this assay presents the biological properties of ustekinumab for stability evaluation.

● [redacted].

● As to the binding of the Fc region of ustekinumab to [redacted] receptor and [redacted] receptor, the 50% effective concentration (EC50) in [redacted] binding assay was approximately [redacted] ng/mL and the 50% inhibitory concentration (IC50) in [redacted] competitive binding assay was [redacted] to [redacted] μg/mL.

2.A.(2).2) Product-related substances

[redacted].

● [redacted].

● Since heavy chain C-terminal Lys residues are removed immediately by enzyme in serum or plasma, the presence or absence of C-terminal Lys residues of the heavy chain is not considered to have an impact on the potency, efficacy, or safety of ustekinumab. Thus, the variants produced due to the loss of C-terminal Lys residue of the heavy chain were considered to be product-related substances.

● [redacted].

2.A.(2).3) Impurities

2.A.(2).3).(a) Process-related impurities

[redacted]. All the process-related impurities have been demonstrated to be consistently and adequately removed in the manufacturing process [see "2.A.(1).3) Manufacturing process"].

2.A.(2).3).(b) Product-related impurities

[redacted]. Based on the results of assessment of the capacity of the manufacturing process to remove impurities, aggregates have been demonstrated to be removed consistently in the manufacturing process [see "2.A.(1).3) Manufacturing process"].

2.A.(2).4) Drug substance specifications

[redacted].

2.A.(2).5) Stability of drug substance

Using manufacturing-scale batches of drug substance, long-term testing ([redacted]°C [redacted] months, 4 batches; [redacted] months, 3 batches; [redacted] months, 2 batches] and [redacted]°C [redacted] months, 4 batches]), intermediate testing ([redacted]°C [redacted] months, 3 batches; [redacted] months, 2 batches; [redacted] months, 4 batches]), and accelerated testing ([redacted]°C [redacted] months, 9 batches]) were conducted. In all the studies, polycarbonate bottles with polypropylene caps were used to store drug substance samples.

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[redacted]

At the long-term storage condition, no changes over time occurred throughout the testing period at either [redacted]°C or [redacted]°C, except for a transient increase in potency at [redacted] months for [redacted] batches stored at [redacted]°C. In the intermediate storage condition ([redacted]°C), [redacted] batches showed a decrease in potency at [redacted] months of storage, but no other changes over time were observed at ≥[redacted] months of storage. No changes over time occurred for other attributes tested.

Based on the above stability data, a shelf life of [redacted] months was proposed for the drug substance when stored at ≤[redacted]°C.

2.A.(3) Drug product

2.A.(3).1) Formulation development

[redacted]. The proposed product is supplied in a prefilled glass syringe with a stainless needle and each prefilled syringe contains a volume of the drug solution that is sufficient to ensure delivery of 45 mg of ustekinumab. Each prefilled syringe is equipped with a needle safety guard (UltraSafe Passive Delivery System) (needle guard). A carton is used as the secondary packaging.

2.A.(3).2) Drug product manufacturing process

The manufacturing process for the drug product is as shown below.

	Manufacturing process	In-process controls
Step 1	**Thawing of FB**	
Step 2	**Pooling and Mixing**[1)]	Bioburden and Endotoxin
Step 3	[redacted]	Bioburden and Endotoxin
Step 4	**Sterile filtration**	Filter integrity
Step 5	**Filling**[2)]	[redacted]
Step 6	**Assembly**	
Step 7	**Secondary packaging**	
Step 8	**Testing, Storage**	

1): FB is pooled into the mixer (Step 2) within [redacted] hours after start of thawing (Step 1).
2): Filling is started within [redacted] hours after start of pooling of thawed FB (Step 1) into the mixer (Step 2).
Filling is completed within [redacted] hours.

[redacted]. As a result, the pre-determined acceptance criteria were met for all theattributes evaluated or the quality of the drug product was not affected, showing that the drug product of consistent quality can be manufactured. For

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[redacted] batches of another drug product to be supplied in a similar prefilled syringe (with a needle guard), no malfunction of the needle guard fitted in the assembly step was observed. Step [redacted] was defined as a critical step.

2.A.(3).3) Manufacturing process development

A liquid formulation for intravenous administration or a lyophilized formulation for subcutaneous administration was used in foreign phase I and phase II clinical studies. Another liquid formulation for subcutaneous administration was used in foreign phase III and Japanese phase I clinical studies. Furthermore, the liquid formulation for subcutaneous administration in a prefilled syringe (the liquid formulation in a prefilled syringe) was used in a Japanese phase II/III study. The liquid formulation in a prefilled syringe equipped with a needle guard is proposed for marketing.

2.A.(3).4) Drug product specifications

[redacted]

2.A.(3).5) Stability of drug product

Using manufacturing-scale batches of the drug product, long-term testing, accelerated testing, stress testing, photostability testing, and cycle tests were performed. The attributes tested are shown in Table 6.

Table 6. Stability studies on drug product

	Test conditions	Attributes tested
Long-term testing	2°C−8°C (24 months, 5 batches)	[redacted]
Accelerated testing	25°C ([redacted] months, 5 batches)	[redacted]
Stress testing	[redacted]°C ([redacted] months, 5 batches)	[redacted]
Photostability testing	[redacted]°C, an overall illumination of 1.2 million lux·hr and an integrated near ultraviolet energy of 200 W·h/m^2, 1 batch[1)]	[redacted]
Cycle tests	Condition 1[2)] and Condition 2[3)], 2 batches each	[redacted]

[1)] Three types of packaging were used in the study: (a) Primary packaging only (a glass syringe), (b) Primary and Secondary packaging (a carton), (c) Primary and Secondary packaging plus aluminum foil.

[2)] [redacted]

[3)] [redacted]

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[redacted].

[redacted].

[redacted]. No significant changes occurred for other attributes tested throughout the testing period.

[redacted]. In the samples of the drug product with primary and secondary packages compared to the samples of the drug product further wrapped with aluminum foil, changes from the initial time point in the IEF pattern were observed, but when a higher-sensitivity method, cIEF, was used, no changes in the cIEF pattern were noted, nor were any changes observed for other attributes tested.

Cycle tests were performed to evaluate the effect of short-term excursions outside the predetermined temperature range during shipping, storage, and use of the product. In the cycle test 1, a slight decrease in potency was observed after [redacted] cycles, but no significant changes were observed for other attributes tested throughout the testing period. In the cycle test 2, no significant changes were observed for the tested attributes throughout the testing period.

Based on the above stability data, a shelf life of 18 months was proposed for the drug product when stored at 2°C to 8°C and protected from light.

2.A.(4) Reference materials

[redacted]

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[redacted]

[redacted].

2.B Outline of the review

PMDA reviewed the submitted data, including the following major considerations, and concluded that the quality of the product is adequately controlled.

2.B.(1) Safety of non-human glycan structures

Non-human glycan structures are present in ustekinumab: sialylated oligosaccharides containing a non-human sialic acid NGNA ([redacted]% of the total glycans) and oligosaccharides containing a non-human Galα1-3Gal. PMDA asked the applicant to explain whether there is a safety concern about administering ustekinumab containing these non-human glycan structures.

The applicant explained as follows:

The glycans of ustekinumab are constrained in the internal cavity enclosed by the two polypeptide backbones of the CH2 domains of the Fc region and sterically shielded so that other molecules have limited access to these glycans. Therefore, these glycans are not considered to be antigenic or immunogenic (Dalziel M, McFarlane I, Axford JS., *Glycoconj J*. 1999;16: 801-7). Based on the clinical experience with ustekinumab in >2000 patients in Japan and overseas, no allergy-related serious adverse events after the initial or repeated doses have been reported and the incidence of anti-ustekinumab antibody development was low, suggesting that oligosaccharides containing NGNA or Galα1-3Gal in ustekinumab are unlikely to be antigenic or immunogenic.

PMDA accepted the above response.

2.B.(2) Measures to prevent contamination

During the process validation, 1 batch was found to be contaminated with *Staphylococcus epidermidis* on Day [redacted] of cell culture for production. PMDA asked the applicant to explain the cause of the contamination and the measures to prevent the contamination.

The applicant explained as follows:

It seemed that the contamination was caused by leakage of media after the bioreactor was improperly connected to the media container. As a measure to prevent the contamination, the employees were

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retrained on the connecting procedures. Nine batches produced on a commercial manufacturing scale after 2007 were all free of such contamination.

Based on the manufacturing history, PMDA concluded that another contamination of this kind is unlikely to occur in future production and accepted the above response.

2.B.(3) Drug substance specifications

PMDA requested the applicant to include in the drug substance specifications a test intended to detect a structural change without charge variation and to directly assess the consistency of the structure of ustekinumab, including heterogeneity due to post-translational modifications etc.

The applicant responded that peptide mapping will be included in the drug substance specifications in order to assure the consistency of the structure of ustekinumab, including heterogeneity.

PMDA accepted the above response.

2.B.(4) Needle guard fitted to syringe

PMDA asked the applicant to explain the possibility that the needle guard fitted to the syringe is activated improperly during the use of the product.

The applicant responded as follows:

In foreign countries, no adverse events related to product malfunctions have been reported to date. The following malfunction is most likely to occur: the entire prefilled syringe contents have not been injected and as a result, the needle guard is not activated. However, such a malfunction does not cause adverse events to patients or healthcare providers. An illustrated explanation on how to use the needle guard will be included in the package insert, as a guide to healthcare providers.

PMDA accepted the above response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

As the primary pharmacodynamic studies of ustekinumab, the binding of ustekinumab to IL-12 and IL-23, inhibition of IL-12 and IL-23 binding to their receptors, inhibition of IL-12 and IL-23 bioactivity, and species binding and neutralization activity were determined. As the reference data, the results from a study using a murine model of psoriasis were submitted. As the secondary pharmacodynamic studies, its effects on asthma and its cross-reactivity with normal human tissues were studied. Although no safety pharmacology studies have been performed, the effects of ustekinumab on the functions listed in the safety pharmacology core battery were investigated based on the data from 26-week and 4-week repeat-dose toxicity studies in cynomolgus monkeys, in

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accordance with the ICH guidelines. Ustekinumab derived from the cell line B cultured in medium containing bovine fetal serum was used in pharmacology studies, but, in some studies, ustekinumab derived from the cell line C or ustekinumab derived from the cell line D cultured in serum-free medium were used instead. No pharmacodynamic drug interaction studies have been performed.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Binding to human IL-12 and IL-23 (4.2.1.1.1)

3.(i).A.(1).1).(a) Binding to IL-12, IL-23, and IL-12/23p40

The binding of ustekinumab to human IL-12, IL-23, or IL-12/23p40 ([redacted] µg/mL) was determined by ELISA. Ustekinumab was shown to have comparable binding to each of IL-12, IL-23, and IL-12/23p40.

n**3.(i).A.(1).1).(b) Binding to proteins related to IL-12/23p40**

3.(i).A.(1).1).(b) Binding to proteins related to IL-12/23p40

The binding of ustekinumab to the following proteins was determined by dot blotting: IL-12; IL-12/23p40; IL-6; IL-6 receptor (IL-6sR) and ciliary neurotrophic factor receptor (CNTFR), which are structurally related to IL-12/23p40; and the fusion protein of antibody crystallizable fragment (Fc) and IL-11 receptor, which is functionally related to IL-12/23p40 (IL-11R/Fc). Ustekinumab bound to IL-12 and IL-12/23p40, but not to IL-6, IL-6sR, CNTFR, or IL-11R/Fc.

3.(i).A.(1).1).(c) Crystal structure analysis

X-ray crystallographic analysis of ustekinumab Fab/IL-12 complex, formed by the reaction of the antigen-binding fragment (Fab) of ustekinumab with deglycosylated IL-12, showed that the variable domain fragment (Fv) of ustekinumab binds to the epitope in the D1 domain of IL-12/23p40 comprised of three domains (D1-D3), and that the epitope is distant from IL-12p35 (IL-12 consists of IL-12/23p40 and IL-12p35 subunits). The applicant explained that since IL-23p19 overlaps well with IL-12p35 (IL-23 consists of IL-12/23p40 and IL-23p19 subunits) (Beyer BM et al. *J Mol Biol.* 2008;382:942-55), it is believed that also in the case of IL-23, ustekinumab binds to the epitope in the D1 domain of IL-12/23p40 and that the D1 domain is distant from IL-23p19.

3.(i).A.(1).1).(d) Binding epitope analysis

The amino acid residues of IL-12/23p40 involved in the binding to ustekinumab were identified by binding epitope analysis, using protein variants with amino acid residues mutated in the D1 domain. Introduction of mutations using site-directed mutagenesis resulted in reduced binding to ustekinumab, indicating that M23, L40, S43, E45, E59, and D62 are the amino acid residues of IL-12/23p40 involved in the binding to ustekinumab.

3.(i).A.(1).1).(e) Analysis of binding affinity

The equilibrium constants (K_D) for ustekinumab binding to IL-12 and IL-23 as determined by surface plasmon resonance, were [redacted] and [redacted] pmol/L ([redacted] and [redacted] µg/mL), respectively.

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3.(i).A.(1).1).(f) Stoichiometric analysis

The stoichiometry of ustekinumab binding to IL-12 or IL-23 was conducted by isothermal titration calorimetry. Human IL-12 and IL-23 bound to ustekinumab at ratios of 2:0.94 and 2:0.92, respectively, showing the expected ligand to antibody ratio of 2:1.

3.(i).A.(1).2) Inhibition of human IL-12 and IL-23 binding to their receptors (4.2.1.1.2)

3.(i).A.(1).2).(a) Inhibition of binding to IL-12 receptor β-1 (IL-12Rβ1)

Human IL-12 or IL-23 ([redacted] ng/mL each) was reacted with ustekinumab ([redacted] ng/mL), which was added to IL-12Rβ1/Fc fusion protein. Ustekinumab demonstrated equivalent inhibition of IL-12 and IL-23 binding to IL-12Rβ1/Fc.

3.(i).A.(1).2).(b) Inhibition of binding to receptor complexes IL-12Rβ1/β2 and IL-12Rβ1/23R

Human IL-12 or IL-23 was reacted with ustekinumab or anti-IL-12/23p40 mAb (C8.3) that recognizes a different epitope than ustekinumab and that has no neutralization activity, which was added to the IL-12 responsive cell line (H) or the IL-23 responsive cell line (NKL). Ustekinumab inhibited IL-12 and IL-23 from binding to H cells and NKL cells, respectively, whereas IL-12/23p40 mAb with no neutralization activity did not inhibit IL-12 or IL-23 from binding to the cells.

Based on the above, the applicant explained that ustekinumab was shown to inhibit IL-12 and IL-23 from binding to their receptor complexes expressed on the cell membrane.

3.(i).A.(1).2).(c) Binding ability to IL-12 and IL-23 already bound to receptors

Human IL-12 or IL-23 was reacted with H cells or NKL cells and added with ustekinumab or anti-IL-12/23p40 mAb (G) with no neutralization activity. While G was detected on the cell surface, ustekinumab was not detected on the cell surface.

Based on the above, the applicant inferred that ustekinumab cannot bind to IL-12 or IL-23 that is already bound to receptor complexes on the cell surface.

3.(i).A.(1).2).(d) CDC activity

Human peripheral blood lymphocytes (PBL) activated by phytohemagglutinin (PHA) were added with human IL-12 and ustekinumab [redacted] μg/mL and treated with complement. Ustekinumab did not induce CDC of PHA-activated PBL.

3.(i).A.(1).3) Inhibition of IL-12-mediated Th1 cellular response and IL-23-mediated Th17 cellular response (4.2.1.1.3)

3.(i).A.(1).3).(a) Effects on intracellular signaling

The effects of ustekinumab on IL-12-mediated intracellular signaling were determined by flow cytometry. Ustekinumab ([redacted] or [redacted] μg/mL) was reacted with human IL-12 or IL-23 ([redacted] ng/mL each), which was added to NKL cells. Ustekinumab inhibited IL-12-mediated phosphorylation

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of signal transducers and activators of transcription STAT4 and STAT6 and IL-23-mediated phosphorylation of STAT3.

3.(i).A.(1).3).(b) Effects on the expression of cell surface markers

The effects of ustekinumab on IL-12-mediated expression of cell surface markers were determined by flow cytometry. Human IL-12 ([redacted] ng/mL) was reacted with PHA-activated human peripheral blood mononuclear cells and added with ustekinumab (derived from the cell line B) [redacted] μg/mL. Ustekinumab inhibited the otherwise increased IL-12-mediated expression of IL-12 receptor β-2 (IL-12Rβ2) and cutaneous lymphocyte antigen (CLA).

3.(i).A.(1).3).(c) Effects on cytokine production

The effects of ustekinumab on IL-12-mediated cytokine production were determined by ELISA. Ustekinumab (derived from the cell line C) or ustekinumab Fab ([redacted] nmol/L) was reacted with human IL-12 ([redacted] ng/mL), which was added to PHA-activated human T cell blasts. Both ustekinumab and ustekinumab Fab inhibited IFN-γ mRNA expression.

The effects of ustekinumab on IL-23-mediated cytokine production were determined by ELISA. [redacted]

When ustekinumab ([redacted] μg/mL) and human IL-23 ([redacted] ng/mL) were added to NKL cells and incubated in the presence of IL-2 and anti-IFN-γ antibodies, ustekinumab inhibited the production of IL-10.

3.(i).A.(1).4) Species binding and neutralization activity (4.2.1.1.4)

3.(i).A.(1).4).(a) Neutralization activity against IL-12 and IL-23 from different species

The neutralization activity of ustekinumab against IL-12 and IL-23 from different species was determined by ELISA and RT-PCR. Cytokine-containing culture supernatants prepared from adherent cells in the peripheral blood mononuclear cells or splenocytes from humans, chimpanzees, baboons, cynomolgus monkeys, marmosets, rhesus monkeys, dogs, rabbits, rats, and mice, and serially diluted ustekinumab solutions were added to PHA-activated T cells of the respective species, and IL-12-mediated IFN-γ mRNA expression and IFN-γ protein production and IL-23-mediated IL-17A protein production were used as measures of neutralization activity. Ustekinumab neutralized human, chimpanzee, baboon, cynomolgus monkey, marmoset, and rhesus monkey IL-12, but showed little activity to dog and rabbit IL-12 and no activity to rat and mouse IL-12. Ustekinumab neutralized human, chimpanzee, baboon, cynomolgus monkey, and rhesus monkey IL-23, but showed partial activity to dog IL-23 and no activity to rat and mouse IL-23.

3.(i).A.(1).4).(b) Binding to and neutralization activity against recombinant cynomolgus monkey IL-12 and IL-23

Recombinant cynomolgus monkey IL-12 or IL-23 was added with ustekinumab. Ustekinumab was

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shown to have comparable binding to human and cynomolgus monkey IL-12 and IL-23. [redacted].

Ustekinumab derived from the cell line C and that from the cell line D were compared for their neutralization activity against recombinant cynomolgus monkey IL-12. They showed comparable inhibition of cynomolgus monkey IL-12 ([redacted] ng/mL)-mediated IFN-γ production from H cells.

3.(i).A.(1).4).(c) Neutralization activities of anti-mouse IL-12/23p40 antibody and ustekinumab against mouse IL-12 and IL-23

[redacted].

3.(i).A.(1).5) Effects in a murine model of psoriasis (Reference data 4.2.1.1.5)

Psoriasis-like symptoms were induced in severe combined immunodeficiency (SCID) mice (n = 10/group) by intraperitoneal transfer of $CD4^{+}CD45RB^{hi}CD25^{-}$ cells isolated from BALB/cBy mouse splenocytes and 7 and 35 days after the cell transfer, the mice were treated intraperitoneally with 0.5 mg of anti-mouse IL-12/23p40 antibody. Compared to the negative control antibody, anti-mouse IL-12/23p40 antibody significantly reduced the mean severity score, reduced acanthosis and rete ridges (downgrowth to the basal layer), and inhibited inflammatory cell infiltration, and significantly reduced the expression of IL-23p19, IL-1α, IL-6, IL-17A, IL-17F, and IL-22 mRNA and tended to reduce the expression of IFN-γ, TNF-α, and IL-12p35 mRNA in skin tissues.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Effects of ustekinumab in a model of asthma in cynomolgus monkeys (a pilot study) (4.2.1.2.2)

In a model of asthma in cynomolgus monkeys, the effects of IL-12 inhibition by ustekinumab on the exacerbation of asthma were studied. Cynomolgus monkeys (n = 2/group) with positive bronchoconstrictor responses to inhaled *Ascaris suum* antigen were intravenously given ustekinumab (9 or 45 mg/kg) 3 weeks later and then challenged with the antigen 1 hour later. Compared to the changes following the initial antigen challenge before ustekinumab treatment, ustekinumab did not affect pulmonary resistance, dynamic compliance, or cellular composition in bronchoalveolar lavage fluid (BALF). At 4 weeks after the first dose, 1 of the cynomolgus monkeys treated with ustekinumab at 45 mg/kg was given the same dose of ustekinumab followed by antigen challenge in the same manner. As a result, an increased bronchoconstrictor response and an increase in eosinophil count in the BALF were observed.

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3.(i).A.(2).2) Effects of ustekinumab in a model of asthma in cynomolgus monkeys (a confirmatory study) (4.2.1.2.3)

Cynomolgus monkeys (n = 4/group) with positive bronchoconstrictor responses to *Ascaris suum* antigen were given ustekinumab at 45 mg/kg prior to antigen challenge on two occasions, in the same manner as in the pilot study. Compared to the changes following the initial antigen challenge before ustekinumab treatment, administration of ustekinumab on two occasions did not affect the bronchoconstrictor response or eosinophil count in the BALF following antigen challenge.

3.(i).A.(2).3) Cross-reactivity with normal human tissues (4.2.1.2.4)

Using cryosections of normal human tissues[3], cross-reactivity of ustekinumab with normal human tissues was studied by immunohistochemical staining. Ustekinumab did not cross-react with any of the normal human tissues tested.

3.(i).B Outline of the review by PMDA

PMDA asked the applicant to sort out the latest findings on the association between psoriasis and IL-12/IL-23, and the data from non-clinical and clinical studies of ustekinumab, etc. and to discuss in details the mechanism of action of ustekinumab in the treatment of psoriasis.

The applicant explained as follows:

(a) The activation of Th1 and Th17 cells by IL-12 and IL-23, respectively, is believed to play a key role in the development of psoriasis (Nestle FO, Conrad C. *J Invest Dermatol* 2004;123:xiv-xv, Lew W, Bowcock AM, Krueger JG. *Trends Immunol.* 2004;25:295-305, Nickoloff BJ. *Nat Med.* 2007;13:242-4), (b) IL-12 is believed to promote induction of differentiation from $CD4^+$naïve T cells to Th1 cells and activation of natural killer (NK) cells, production of cytokines such as IFN-γ from Th1 and NK cells, and the expression of CLA in inflammatory sites and thereby induces accumulation of T cells in skin lesions of psoriasis and epithelial cell proliferation, leading to the exacerbation of psoriasis (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68), (c) IL-23 induces the production of cytokines such as IL-17 and IL-22 from Th17 cells and these cytokines are believed to induce psoriatic lesions such as epidermal thickening (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68, Zheng Y et al. *Nature.* 2007;445:648-51), (d) Increased expressions of IL-12 and IL-23 genes and proteins in the lesional skin and serum of patients with psoriasis have been reported (Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-68, Roussaki-Schulze AV et al. *Int J Clin Pharmacol Res*. 2005;xxv:169-73, Chan JR et al. *J Exp Med*. 2006;203:2577-87) and psoriasis therapies such as cyclosporine, narrow-band UVB phototherapy, and anti-TNF therapy have been found to regulate the levels of IL-12 and IL-23 (Torti DC, Feldman SR. *J Am Acad Dermatol*. 2007;57:1059-68), and (e) Single-nucleotide polymorphisms in the IL-12B gene encoding the IL-12/23p40 subunit and the gene encoding the IL-23 receptor subunit have been identified to be associated with psoriasis susceptibility (Cargill M et al. *Am J Hum Genet*. 2007;80:273-90). Taking

[3] Including all normal human tissues as recommended in "Points to Consider in the Manufacture and Testing of Monoclonal Products for Human Use (FDA/CBER)".

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account of these findings, IL-12 and IL-23 are considered to play a very important role in the pathogenesis of psoriasis.

As Foreign Study C0379T01 showed that mRNA expression levels of cytokines produced by activated Th1 cells were reduced in psoriatic skin lesions in patients treated with ustekinumab (Toichi E, et al. *J Immunol*. 2006;177:4917-26), it is inferred that the activation of Th1 and Th17 cells is inhibited *in vivo* as well and it is discussed that ustekinumab inhibits the activation of Th1 and Th17 cells by IL-12 and IL-23, respectively, in the psoriatic skin lesions and draining lymph nodes as observed *in vitro* and exerts its therapeutic effects through the reduction of the expression of cytokines, chemokines, and adhesion molecules etc. involved in the pathogenesis of psoriasis.

Based on the submitted data and responses etc., PMDA concluded that the pharmacological effects of ustekinumab via IL-12/23p40 have been demonstrated and that ustekinumab can be expected to be effective in the treatment of psoriasis.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The pharmacokinetics of ustekinumab administered subcutaneously or intravenously were investigated in cynomolgus monkeys. Ustekinumab concentrations in the serum and milk were determined by enzyme-linked immunosorbent assay (ELISA) with human IL-12 adsorbed onto the plate and electrochemiluminescent immunoassay (ECLIA) using monoclonal antibodies against the variable region of ustekinumab (lower limit of quantification, 0.09-0.17 μg/mL [ELISA]; 0.09 μg/mL [ECLIA]), respectively. Anti-ustekinumab antibodies were detemined by ELISA. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean ± standard deviation (SD).

3.(ii).A.(1) Absorption

3.(ii).A.(1).1 Single-dose studies (4.2.2.2.1 to 4.2.2.2.2)

The pharmacokinetic parameters after a single subcutaneous or intravenous administration of ustekinumab in male cynomolgus monkeys were as shown in Table 7. The bioavailability of subcutaneous ustekinumab was estimated to be ≥90% by comparison of the AUC_∞ values of single-dose subcutaneous and intravenous studies using the same dose of ustekinumab.

Table 7. Pharmacokinetic parameters of ustekinumab after single-dose administration to cynomolgus monkeys

Dose (mg/kg)	Route	n	C_{max} (μg/mL)	t_{max} (day)	AUC_∞ (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	Vd_z (mL/kg)
0.9	s.c.	3	8.16 ± 1.69	3 (3-7)	131.18 ± 86.00	4.71 ± 4.67	-	-
0.9	i.v.	3	25.57 ± 5.80	-	138.24 ± 27.02	7.58 ± 1.68	6.7 ± 1.5	70.1 ± 19.0
9	i.v.	3	436.50 ± 48.36	-	2452.50 ± 396.54	12.10 ± 1.33	3.7 ± 0.6	60.4 ± 13.2

Mean ± SD except for t_{max}, Median (Min-Max) for t_{max}, C_{max}: maximum serum concentration, t_{max}: time to reach the maximum serum concentration,
AUC_∞: area under the serum concentration-time curve from time zero to infinite time, $t_{1/2}$: elimination half-life, CL: total body clearance, Vd_z: volume of distribution at the terminal phase

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3.(ii).A.(1).2) Repeat-dose studies (4.2.3.6.1, 4.2.3.5.1.1, 4.2.3.2.1)

Male and female cynomolgus monkeys (n = 2/sex) were subcutaneously administered 45 mg/kg of ustekinumab twice weekly for 3 weeks. The trough serum concentration of ustekinumab increased with each dose. The C_{max} after the first dose was 349.29 ± 32.51 μg/mL and the C_{max} after the last (the 6th) dose was 2460.02 ± 649.57 μg/mL and ustekinumab was eliminated with a $t_{1/2}$ of 16.31 ± 6.62 days after the last dose.

Male cynomolgus monkeys (n = 6/group) were subcutaneously administered 22.5 or 45 mg/kg of ustekinumab twice weekly for 13 weeks. The C_{max} values after the first dose were 262.57 ± 57.37 and 387.72 ± 111.96 μg/mL, respectively, the C_{max} values after the last (the 26th) dose were 2598.54 ± 702.50 and 3781.85 ± 1322.19 μg/mL, respectively, and ustekinumab was eliminated with a $t_{1/2}$ of 19.88 to 21.93 days (median) after the last dose. The AUCs from time 0 to 91 days after the last dose were 65,174.02 ± 34,807.11 and 86,668.58 ± 37,837.40 μg·day/mL, respectively.

Male and female cynomolgus monkeys (n = 8/sex/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly for 26 weeks. The C_{max} values after the first dose were 370.11 ± 197.51 and 672.64 ± 366.79 μg/mL, respectively, the AUCs from time 0 to 3 days after administration (AUC_{3day}) were 765.25 ± 436.75 and 1424.23 ± 700.72 μg·day/mL, respectively, the C_{max} values after the last (the 52nd) dose were 1419.13 ± 493.65 and 2347.08 ± 660.48 μg/mL, respectively, and the AUC_{3day} values were 3660.79 ± 1060.79 and 6185.90 ± 1500.47 μg·day/mL, respectively, and ustekinumab was eliminated with $t_{1/2}$ values of 13.27 ± 4.30 and 11.60 ± 1.95 days, respectively, after the last dose. Trough serum concentrations of ustekinumab were constant after Day 71, which demonstrated that steady-state is reached by Week 13.

The C_{max} and AUC_{∞} values after a single subcutaneous dose of ustekinumab and after the first dose in a subcutaneous repeat-dose study increased in an almost dose-proportional manner.

The applicant explained about a longer $t_{1/2}$ after multiple-dose administration compared to single-dose administration as follows:

It is inferred that the clearance observed after single-dose administration was accelerated due to the development of anti-ustekinumab antibodies. The $t_{1/2}$ was not substantially different between single- and multiple-dose administrations, and there should be no possibility of higher accumulation of ustekinumab after multiple dosing than predicted from that after single-dose administration.

3.(ii).A.(1).3) Comparability studies (4.2.2.2.3 to 4.2.2.2.4)

As two different ustekinumab-producing cell lines (B and D) and two different formulations (liquid and lyophilized formulations) were used during pharmaceutical development, single-dose studies in monkeys were conducted to evaluate the comparability of the pharmacokinetic profile of ustekinumab between batches of material produced by the two different cell lines and between the two different formulations.

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Male cynomolgus monkeys (n = 12/group) received a single subcutaneous dose of 9 mg/kg of ustekinumab derived from the cell line B or D. The C_{max} (98.08 ± 22.59 and 82.17 ± 13.75 μg/mL, respectively) and AUC_{∞} (2377.71 ± 718.07 and 2226.15 ± 688.33 μg·day/mL, respectively) were comparable between the two groups and the t_{max}, $t_{1/2}$, CL/F, Vd_z/F, and MRT were also comparable.

Male cynomolgus monkeys (n = 15/group) received a single intravenous dose of 4.5 mg/kg of a lyophilized or liquid formulation of ustekinumab and the C_{max} (49.12 ± 24.25 and 45.30 ± 19.74 μg/mL, respectively) and AUC_{∞} (764.90 ± 233.99 and 792.16 ± 195.94 μg·day/mL, respectively) were comparable between the two groups and the $t_{1/2}$, CL, and Vd_z were also comparable.

3.(ii).A.(2) Distribution

No distribution studies of ustekinumab have been conducted because ustekinumab is a fully human IgG monoclonal antibody and generally, cellular uptake of a biological macromolecular drug is not high and the tissue distribution of ustekinumab is considered limited based on its volume of distribution, target proteins, and cross-reactivity with normal human tissues, etc. Fetal transfer studies were conducted using unlabeled ustekinumab.

3.(ii).A.(2).1) Fetal transfer (4.2.3.5.2.1 to 4.2.3.5.2.2)

Pregnant cynomolgus monkeys (n = 12/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to gestation day 51. The maternal serum ustekinumab concentrations on gestation days 100 to 102 were 45.24 ± 37.30 and 55.65 ± 16.63 μg/mL, respectively, and the fetal serum ustekinumab concentrations were 16.56 ± 12.32 and 21.56 ± 10.22 μg/mL, respectively.

Pregnant cynomolgus monkeys (n = 12/group) were intravenously given 9 or 45 mg/kg of ustekinumab once weekly from gestation day 20 to gestation day 48. The maternal serum ustekinumab concentrations on gestation day 100 were 19.13 ± 9.47 and 54.47 ± 31.13 μg/mL, respectively, and the fetal serum ustekinumab concentrations were 8.39 ± 4.29 and 19.14 ± 10.64 μg/mL, respectively.

3.(ii).A.(3) Metabolism and excretion

No metabolism and excretion studies of ustekinumab have been conducted because ustekinumab is a fully human IgG monoclonal antibody and is degraded into peptides and amino acids and excreted or recycled via pathways in the same manner as endogenous IgG in humans. A study of excretion into milk was conducted.

3.(ii).A.(3).1) Excretion into milk (4.2.3.5.3.1)

Pregnant cynomolgus monkeys (n = 20/group) were subcutaneously given 22.5 or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to lactation day 33. The ustekinumab concentrations in milk on lactation day 14 (2 days after administration) were 1.43 ± 0.45 and 3.12 ± 1.66 μg/mL,

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respectively, and the ustekinumab concentrations in milk on lactation day 28 (2 days after administration) were 1.64 ± 0.48 and 3.18 ± 1.71 μg/mL, respectively.

3.(ii).B Outline of the review by PMDA

PMDA asked the applicant to explain the relationship of IL-12 and IL-23 with the expression of cytochrome p450 (CYP) enzymes.

The applicant explained as follows:
Although there has so far been no report that IL-12/23 affects CYP enzyme expression, some cytokines such as IL-6 and IL-1β have been reported to down-regulate the expression of various CYPs (Abdel-Razzak Z et al. *Mol Pharmacol*. 1993;44: 707-15), and the relationship between IL-12/23 and CYP cannot be denied, nor are there data regarding ustekinumab interactions with drugs that are metabolized by CYP enzymes. Thus, an *in vitro* study to determine the effect of IL-12/23 on CYP enzyme expression is currently ongoing.

PMDA considers as follows:
As it is also envisaged that ustekinumab will be used in combination with CYP substrates such as cyclosporine for the treatment of psoriasis, it is necessary to complete the above study as soon as possible and appropriately provide the obtained information to healthcare providers in clinical settings.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of ustekinumab conducted were repeat-dose toxicity, reproductive and developmental toxicity, and local tolerance studies. Safety pharmacology endpoints and immunotoxicity measurements were incorporated in the toxicity studies. No anti-ustekinumab antibodies were detected in the animals used in the toxicity studies and ustekinumab exposure has been confirmed to be maintained during the dosing period in all studies.

3.(iii).A.(1) Single-dose toxicity (4.2.2.2.1 to 4.2.2.2.2, 4.2.3.2.1)

No single-dose toxicity studies have been conducted. Single-dose toxicity was evaluated based on the data from single subcutaneous dose and single intravenous dose pharmacokinetic studies in cynomolgus monkeys (4.2.2.2.1 to 4.2.2.2.2) and the data after the first dose in a 26-week subcutaneous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.1). No mortality occurred and no ustekinumab-related effects were observed for clinical observations, body weight, or food consumption up to the high dose of 9 mg/kg in the pharmacokinetic studies and up to the high dose of 45 mg/kg in the 26-week subcutaneous repeat-dose toxicity study (observation after the first dose).

3.(iii).A.(2) Repeat-dose toxicity

As repeat-dose toxicity studies, a 26-week subcutaneous dose toxicity study and a 4-week intravenous dose toxicity study in cynomolgus monkeys were conducted. In the 26-week subcutaneous dose

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toxicity study, an animal in the high dose group had diarrhoea, body weight loss, and elevated white blood cell count, etc., which were considered to be associated with bacterial enteritis, were observed and their relationship to ustekinumab could not be denied. The AUC_{72h} and C_{max} of ustekinumab (after the last dose) at the no-observed-adverse-effect level (NOAEL) (45 mg/kg) in the 26-week subcutaneous dose toxicity study in cynomolgus monkeys were approximately 22-fold the AUC_{∞} after single-dose administration and approximately 116-fold the C_{max} after 4 weeks of once-weekly subcutaneous administration (after the 4th dose) to humans at the maximum recommended clinical dose of 90 mg in a foreign phase II study (Study C0379T04).[4]

3.(iii).A.(2).1) Twenty-six-week subcutaneous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.1)

Cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly for 13 or 26 weeks. In this study, as immunological tests, peripheral blood lymphocyte subset analyses ($CD2^+$, $CD3^-$, $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD14^+$, $CD16^+$, $CD20^+$, $CD45^+$) were performed and anti-keyhole limpet hemocyanin (KLH) antibody response was measured following intramuscular injection of KLH in incomplete Freund's adjuvant on Days 14 and 30. One of 16 animals in the 22.5 mg/kg group had ventricular extrasystoles, which were considered coincidental and unrelated to ustekinumab. At Week 26, 1 of 16 animals in the 45 mg/kg group had diarrhoea, body weight loss, and elevated white blood cell count and hyperplasia of the myeloid cells and acute inflammation in the ileum, which were considered to be associated with bacterial enteritis. Although their relationship to inhibition of IL-12 and IL-23 by ustekinumab could not be denied, no findings indicative of immunotoxicity were observed in this animal and immunosuppression by ustekinumab was not suggested in the other dose group or other toxicity studies. Thus, bacterial enteritis may have been coincidental. In the immunological test, peripheral blood lymphocyte subset analyses showed changes in the percentages of $CD45^+$, $CD16^+$, and $CD2^+$ in animals treated with ustekinumab, but these changes were small and were not considered of toxicological significance. KLH analysis showed that anti-KLH antibody titers for male animals in the 45 mg/kg group tended to decrease, which was not considered of toxicological significance because this finding occurred in males only and animal to animal variation in anti-KLH antibody response was observed. The NOAEL was determined to be 45 mg/kg. Safety pharmacology evaluations revealed no ustekinumab-related effects on the cardiovascular, central nervous, or respiratory system.

3.(iii).A.(2).2) Four-week intravenous repeat-dose toxicity study in cynomolgus monkeys (4.2.3.2.3)

Cynomolgus monkeys were intravenously given 0 (saline), 9, or 45 mg/kg of ustekinumab once weekly for 4 weeks. In the 45 mg/kg group, 1 of 10 animals had ventricular extrasystoles and on Day

[4] The AUC or C_{max} of ustekinumab administered at the proposed dosage regimen in Japanese patients with psoriasis was not calculated. The trough concentration at the NOAEL (45 mg/kg) in a 26-week subcutaneous dose toxicity study in cynomolgus monkeys after the last dose (Day 166) was 531-fold (maximum) or 2125-fold (median) the trough concentration at Week 64 in Japanese patients with psoriasis administered ustekinumab at the maximum recommended clinical dose of 90 mg at Weeks 0 and 4 and then every 12 weeks (Study JPN-02).

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28 (6 days after the 4th dose), compared to the control group, its relative lymphocyte counts decreased and its absolute and relative neutrophil counts increased. The ventricular extrasystoles were considered coincidental and unrelated to ustekinumab. When the lymphocyte and neutrophil values, etc., were compared with their pre-dose values, only 1 of the 10 animals showed a marked decrease in relative lymphocyte counts and a marked increase in relative neutrophil counts, and lymphocyte and neutrophil values for the other animals were almost unchanged from their pre-dose values. The lymphocytes or neutrophils on Days 9 and 58 were unaffected and moreover, no changes were observed in males. Therefore, these changes were not considered of toxicological significance. There were no ustekinumab-related effects on other parameters including immunotoxicity endpoints. The NOAEL in this study was determined to be 45 mg/kg. Safety pharmacology evaluations revealed no ustekinumab-related effects on the cardiovascular, central nervous, or respiratory system.

3.(iii).A.(3) Genotoxicity

Since ustekinumab is an antibody drug and there should be little concern about genotoxicity, no genotoxicity studies have been conducted.

3.(iii).A.(4) Carcinogenicity

Ustekinumab does not neutralize IL-12 or IL-23 from mice or rats, which are commonly used in carcinogenicity studies, and although anti-mouse IL-12/23p40 antibody (CNTO 3913), an antibody analogous to ustekinumab, neutralizes mouse IL-12 and IL-23, the information to be obtained from a carcinogenicity study with CNTO 3913 should be limited. Therefore, no carcinogenicity studies using ustekinumab or the antibody analogous to ustekinumab have been performed.

3.(iii).A.(5) Reproductive and developmental toxicity

A male fertility study in cynomolgus monkeys, a female fertility study with an analogous antibody CNTO 3913 in mice, an embryo-fetal development study in cynomolgus monkeys, and a study for effects on pre- and postnatal development including maternal function in cynomolgus monkeys were conducted by the subcutaneous route of administration. An embryo-fetal development study in cynomolgus monkeys was conducted by the intravenous route of administration. Ustekinumab was not teratogenic and there were no effects on either male or female fertility, parturition, embryo-fetal development, or offspring development in any of the studies. Ustekinumab has been shown to cross the placenta (4.2.3.5.2.1) and be excreted in milk (4.2.3.5.3.1) in cynomolgus monkeys [see "3.(ii).A.(2).1) and 3.(ii).A.(3).1)"].

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation

The levels of IL-12 in seminal plasma of infertile men were lower than those of fertile men and there was significant correlation between the IL-12 levels and the total sperm count and percentage of morphologically normal sperm in the semen (Naz RK et al. *J Androl*. 1998;19:302-307). Thus, a male fertility study in cynomolgus monkeys was conducted.

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3.(iii).A.(5).1).(a) Male fertility study in cynomolgus monkeys (4.2.3.5.1.1)

Male cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly for 13 weeks (9 weeks prior to mating and 4 weeks of mating period). There were no ustekinumab-related effects on clinical observations, body weight and food consumption, semen analysis, mating behavior, or serum testosterone and inhibin B levels. No anti-ustekinumab antibodies were detected. The NOAEL for general and reproductive toxicity was determined to be 45 mg/kg.

3.(iii).A.(5).1).(b) Female fertility study with CNTO 3913 in mice (4.2.3.5.1.2)

Female mice were subcutaneously administered 0 (phosphate-buffered saline), 5, or 50 mg/kg of CNTO 3913 (anti-mouse IL-12/23p40 antibody) or 50 mg/kg of an isotype-matched control monoclonal antibody (CNTO 1322) as the negative control article of CNTO 3913, twice weekly beginning 15 days before mating and continuing through gestation day 7. Cesarean section was performed on gestation day 13 and female fertility was evaluated. Although 1 of 25 dams in the CNTO 3913 50 mg/kg group had total litter loss, as the litter average for nonviable embryos in the CNTO 3913 50 mg/kg group (0.3) was lower than those in the vehicle control (0.8) and negative control article (0.7) groups, the finding was not considered related to CNTO 3913. The NOAEL for general and reproductive toxicity was determined to be 50 mg/kg.

3.(iii).A.(5).2) Embryo-fetal development studies

3.(iii).A.(5).2).(a) Subcutaneous administration study in cynomolgus monkeys (4.2.3.5.2.1)

Pregnant cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly from gestation day 20 to gestation day 51. Hormone concentrations in maternal and fetal serum were measured and as immunological tests, maternal and fetal peripheral blood lymphocyte subset analyses and immunohistochemical analysis of fetal lymphoid tissue were performed. Abortion occurred in 1 of 12 dams in the control group, abortion occurred in 3 of 12 dams and embryo/fetal death occurred in 2 of 12 dams in the 22.5 mg/kg group, and embryo/fetal death occurred in 2 of 12 dams in the 45 mg/kg group. Although the incidence of abortion or embryo/fetal death in the 22.5 mg/kg group (5 of 12 dams, 41.7%) exceeded the laboratory historical control range (mean 8.2%, maximum 20%), the incidence in the 45 mg/kg group (2 of 12 dams, 16.7%) was within the historical control range and no dose-dependency was observed. Abortion or embryo/fetal death did not necessarily occur in animals with high ustekinumab exposure levels. There was no correlation between individual exposure levels and abortion or embryo/fetal death. In addition, an embryo-fetal development study in cynomolgus monkeys by intravenous administration (4.2.3.5.2.2) showed that the incidence of abortion or embryo/fetal death in animals treated with ustekinumab was within the historical control range. Therefore, the findings were not considered related to ustekinumab. Although statistically significant differences between the ustekinumab and control groups were observed for serum hormone concentrations (progesterone, 17β-estradiol, prolactin), these changes were within the laboratory historical control range or transient. There was no relationship between changes in serum hormone concentrations and abortion or embryo/fetal death, and maintenance of pregnancy was not affected. Therefore, these changes were not considered related to ustekinumab.

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Asymmetrically aligned palatal rugae were observed in 1 of 7 fetuses in the 22.5 mg/kg group and 1 of 10 fetuses in the 45 mg/kg group, but were not reported in a study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1) and morphological changes in the palate are commonly observed in adult cynomolgus monkeys and are not associated with dysfunction. Thus, this finding was not considered of toxicological significance. No anti-ustekinumab antibodies were detected in maternal or fetal serum. The NOAEL for maternal and embryo-fetal toxicity was determined to be 45 mg/kg.

3.(iii).A.(5).2).(b) Intravenous administration study in cynomolgus monkeys (4.2.3.5.2.2)

Pregnant cynomolgus monkeys were intravenously given 0 (saline), 9, or 45 mg/kg of ustekinumab once weekly from gestation day 20 to gestation day 48. As immunological tests, maternal and fetal peripheral blood lymphocyte subset analyses and immunohistochemical analysis of fetal lymphoid tissue were also performed. Abortion occurred in 1 of 12 dams each in the 9 mg/kg and 45 mg/kg groups, which was not considered related to ustekinumab because abortion occurred in 1 of 12 dams and embryo/fetal death occurred in 1 of 12 dams also in the control group and the incidence was within the laboratory historical control range (mean 8.2%, maximum 20%), etc.

Asymmetrically aligned palatal rugae were observed in 1 of 11 fetuses in the 9 mg/kg group, but not in the 45 mg/kg group, showing no dose-dependency and this finding was not reported in a study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1) and morphological changes in the palate are commonly observed in adult cynomolgus monkeys and are not associated with dysfunction. Thus, the finding was not considered of toxicological significance. No anti-ustekinumab antibodies were detected in maternal or fetal serum. The NOAEL for maternal and embryo-fetal toxicity was determined to be 45 mg/kg.

3.(iii).A.(5).3) Study for effects on pre- and postnatal development, including maternal function in cynomolgus monkeys (4.2.3.5.3.1)

Pregnant cynomolgus monkeys were subcutaneously given 0 (saline), 22.5, or 45 mg/kg of ustekinumab twice weekly from gestation day 20 through Day 33 after delivery. In the F1 generation, as immunological tests, peripheral blood lymphocyte subset analyses were performed and immunological development was evaluated (measurement of anti-KLH and anti-tetanus toxoid antibodies). In the 22.5 mg/kg group, abortion occurred in 3 of 20 dams, stillbirth occurred in 2 of 20 dams, and fetal death occurred in 1 of 20 dams. In the 45 mg/kg group, abortion occurred in 3 of 20 dams, stillbirth occurred in 1 of 20 dams, and fetal death occurred in 1 of 20 dams. Also in the control group, abortion occurred in 2 of 20 dams and stillbirth occurred in 3 of 20 dams. As there were no differences in incidence between the control and ustekinumab groups, the findings were not considered related to ustekinumab. Necropsies of the stillbirths revealed no macroscopic abnormalities. In the F1 generation, 1 of 16 animals in the 22.5 mg/kg group died on postnatal day 6 and this animal had low body weight, emaciation, and smaller thymus with an almost empty gastrointestinal tract, but

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no death occurred in the 45 mg/kg group and the incidence of neonatal deaths was within the laboratory historical control range (3.7%). Thus, the death was not considered related to ustekinumab. Although 1 of 16 F1 animals in the 45 mg/kg group was sacrificed moribund on Day 1 after birth due to lateral position and the fingertips bitten off by the dam, the tip of the tail of 1 of 18 F1 animals was bitten off by the dam on Day 17 after birth also in the control group. Thus, the finding was not considered related to ustekinumab. In the F1 generation, there were no ustekinumab-related effects including those on immunological test results. In the ustekinumab groups, ustekinumab was present in the offspring and in the breast milk from lactating dams. No anti-ustekinumab antibodies were detected in maternal or offspring serum. The NOAEL for maternal and offspring toxicity was determined to be 45 mg/kg.

3.(iii).A.(6) Local tolerance study in cynomolgus monkeys (4.2.3.6.1)

Cynomolgus monkeys were subcutaneously given 0 (vehicle, [redacted]% sucrose, [redacted]% mol/L sodium phosphate, [redacted]% polysorbate 80) or 45 mg/kg of ustekinumab or 3 mg/kg of intravenous immunoglobulin (IGIV) as the positive control article, twice weekly for 3 weeks. Animals in the ustekinumab and vehicle control groups had minimal to mild edema at the injection site, which resolved within 48 hours after injection and no histopathological findings were observed. It was concluded that local tolerance of subcutaneous injection of ustekinumab is good.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Carcinogenicity

PMDA asked the applicant to explain the carcinogenic risk of ustekinumab and the risk of exacerbation of malignancy.

The applicant explained as follows:

No tumors or preneoplastic lesions were observed in a 26-week subcutaneous dose toxicity study in cynomolgus monkeys (4.2.3.2.1), suggesting no risk of malignancy development with ustekinumab. As for IL-12/23p40, the target molecule of ustekinumab, however, the anti-tumor effect of IL-12 in laboratory animals has been suggested (Brunda MJ et al. *J Exp Med.* 1993;178:1223-1230, Lee JC et al. *Cancer Res.* 2002;62:747-755) and studies using knockout mice and anti-IL-12/23p40 antibody have suggested the exacerbation of malignancy (Langowski JL et al. *Nature.* 2006;442:461-465). Concerning the risk of photocarcinogenicity, there is a report suggesting the exacerbation of UV-induced skin tumors in IL-12/23p40 knockout mice (Maeda A et al. *Cancer Res.* 2006;66:2962-2969). In addition, the possibility that other immunosuppressive biologics and immunosuppressants are associated with the development of malignancies such as lymphoma in a clinical setting cannot be denied. Taking account of these findings, the risk of malignancy development with ustekinumab also cannot be denied.

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3.(iii).B.(2) Risk of immunosuppression

Concerning the findings considered to be associated with bacterial enteritis observed in 1 of 16 cynomolgus monkeys in the 45 mg/kg group in a 26-week toxicity study (4.2.3.2.1), PMDA asked the applicant to explain their relationship to the immunosuppressive effect of ustekinumab and the risk of infections associated with ustekinumab in humans.

The applicant explained as follows:

Although this animal had inflammatory response, immunohistochemical analysis of lymphoid tissue and peripheral blood lymphocyte subset analyses revealed no findings indicative of immunotoxicity and T-cell dependent anti-KLH antibody response was not affected either. Therefore, the applicant considered that there were no effects on the immune function and that an increased susceptibility to infections was not suggested. Moreover, in repeat-dose toxicity (4.2.3.2.1 and 4.2.3.2.3) and reproductive and developmental toxicity (4.2.3.5.2.1 to 4.2.3.5.2.2) studies in cynomolgus monkeys, the results of immunotoxicity evaluations showed that ustekinumab was not associated with immunosuppression and naturally occurring diarrhoea is often observed in cynomolgus monkeys in the control group or during acclimatization as well (Trib GW et al. *Lab Anim*. 1983;17:65-69). Taking account of these findings, bacterial enteritis may have been coincidental and although its relationship to ustekinumab cannot be denied, it is very unlikely to be related to the immunosuppressive effect of ustekinumab.

In patients genetically deficient in factors involved in Th1/Th17 cell activation, such as IL-12/23p40, IL-12Rβ1, IFN-γ receptors 1 and 2, STAT1, and NEMO (NF-κB essential modulator), an increased susceptibility to initial mycobacterial infection and recurrent *Salmonella* infection has been reported (Novelli F et al. *Cytokine Growth Factor Rev.* 2004;15:367-377, Fieschi C et al. *J Exp Med*. 2003;197:527-535, Fieschi C, Casanova JL. *Eur J Immunol*, 2003;33:1461-1464, Filipe-Santos O et al. *Semin Immunol,* 2006;18:347-361), while reports of other infections are limited. Thus, it is inferred that protective immunity against most microorganisms is maintained during treatment with ustekinumab. However, as serious infections have been reported in Japanese and foreign clinical studies [see "4.(ii) Summary of clinical efficacy and safety"], the risk of infections associated with ustekinumab cannot be denied, as in the case of other immunosuppressive biologics.

3.(iii).B.(3) Cardiac effects

Ventricular extrasystoles were observed in 26-week and 4-week toxicity studies in cynomolgus monkeys (4.2.3.2.1 and 4.2.3.2.3). PMDA asked the applicant to explain its relationship to ustekinumab.

The applicant explained as follows:

It has been reported that ventricular extrasystoles were observed in ECG from 5 of 62 normal cynomolgus monkeys (8%) (Medcallum GE et al. *Am J Vet Res.* 1993;54:327-332) and according to reports on ECGs recorded in cynomolgus monkey toxicity studies (Detweiler DK,

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Electrocardiography in toxicology studies. In: Sipes IG, McQueen CA, Gandolfi AJ ed. *Comprehensive toxicology,* UK: Elsevier Science; 1997;95-115), the incidence of arrhythmia and conductance abnormalities in cynomolgus monkeys (n = 4822) was 2.43% (ventricular extrasystoles, 1.24%; right bundle branch block, 1.12%) and compared to these data, the incidence of ventricular extrasystoles in the ustekinumab toxicity studies was not markedly higher. Furthermore, histopathological examination revealed no toxicological findings in cardiac tissue in these toxicity studies, and in a study of cross-reactivity with normal human tissues (4.2.1.2.4), ustekinumab binding to cardiac tissue was not observed and ustekinumab is not thought to induce antibody or CDC of cardiac cells. Therefore, the ventricular extrasystoles observed in these toxicity studies are not considered related to ustekinumab.

PMDA largely accepts the above responses from a toxicological point of view, but considers that the risk of carcinogenicity and infections due to immunosuppression cannot be denied in view of the pharmacological effects of ustekinumab and it is necessary to carefully assess the safety of ustekinumab in clinical use based on clinical study data and post-marketing data etc.

4. Clinical data

4.(i) Summary of clinical pharmacology studies

4.(i).A Summary of the submitted data

As the evaluation data on the pharmacokinetics of ustekinumab, the results from a phase I clinical study in Japanese patients with psoriasis (5.3.3.2.1) and a phase II/III clinical study in Japanese patients with psoriasis (5.3.5.1.2-1) and phase I clinical studies in foreign patients with psoriasis (5.3.3.2.2, 5.3.3.2.3), a phase II clinical study in foreign patients with psoriasis (5.3.5.1.1), and phase III clinical studies in foreign patients with psoriasis (5.3.5.1.3-1 to 5.3.5.1.3-3, 5.3.5.1.4-1 to 5.3.5.1.4-3) and population pharmacokinetic analyses (5.3.3.5.1 to 5.3.3.5.2) and a study of ethnic differences (5.3.3.3.1) etc. were submitted. As the reference data, the results of an analysis of correlation between serum ustekinumab concentration and efficacy in foreign patients with psoriasis (5.3.5.3.1) etc. were submitted. Serum ustekinumab concentrations were determined by an ELISA with human IL-12 adsorbed onto the plate (lower limit of quantification, 0.08 μg/mL) or an ECLIA using monoclonal antibodies against the variable region of ustekinumab (lower limit of quantification, 16.88 ng/mL). Anti-ustekinumab antibodies were measured by an enzyme immunoassay (EIA) and neutralizing antibodies were measured by human IL-12-induced IFN-γ production by NK cells. Unless otherwise specified, the data and pharmacokinetic parameters are expressed as the mean or the mean ± SD.

4.(i).A.(1) Pharmacokinetics in patients with psoriasis

Japanese clinical studies

4.(i).A.(1).1) Single subcutaneous administration study (5.3.3.2.1, Study JNS009-JPN-01 [February 2006 to March 2007])

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A placebo-controlled, randomized, double-blind study was conducted in Japanese patients with psoriasis vulgaris (n = 24, 64.89 ± 9.90 kg). The pharmacokinetic parameters following a single subcutaneous administration of 22.5, 45, or 90 mg of ustekinumab were as shown in Table 8. The increase in C_{max} tended to be more than dose-proportional at doses up to 90 mg and was dose-proportional between doses of 22.5 mg and 45 mg. The AUC_{∞} increased in a dose-proportional manner and the $t_{1/2}$ was almost constant, regardless of dose.

Table 8. Pharmacokinetic parameters following a single subcutaneous administration of ustekinumab to Japanese patients with psoriasis vulgaris

Dose	C_{max} (μg/mL)	$AUC_{0\text{-}84day}$ (μg.day/mL)	AUC_{∞} (μg.day/mL)	t_{max} (day)	$t_{1/2}$ (day)	CL/F (mL/day)	Vz/F (L)
22.5 mg	1.412 ± 0.380	49.93 ± 11.04	70.59 ± 32.29	6.99 (4.0-27.0)	53.48 ± 79.19	364.49 ± 126.50	18.84 ± 17.04
45 mg	3.034 ± 0.636	105.30 ± 34.95	139.87 ± 80.14	10.48 (4.0-14.00)	39.07 ± 41.88	451.29 ± 195.23	18.23 ± 6.82
90 mg	8.507 ± 2.397	222.80 ± 72.67	242.97 ± 78.45	10.49 (4.0-14.00)	24.38 ± 8.30	385.15 ± 170.79	14.41 ± 11.54

Mean ± SD, Median (Min-Max) for t_{max}

4.(i).A.(1).2) Multiple subcutaneous administration study (5.3.5.1.2-1 to 5.3.5.1.2-2, Study JNS009-JPN-02 [March 2008 to March 2010])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in Japanese patients with plaque psoriasis (n = 158, 71.95 ± 14.00 kg). When 45 and 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks, at each sampling timepoint from Week 4 through Week 64, serum ustekinumab concentrations were almost dose-proportional and the trough serum concentrations of ustekinumab (median)[5] were 0.25 and 0.74 μg/mL, respectively, at Week 16, 0.25 and 0.65 μg/mL, respectively, at Week 28, 0.28 and 0.55 μg/mL, respectively, at Week 40, 0.29 and 0.67 μg/mL, respectively, at Week 52, and 0.31 and 0.76 μg/mL, respectively, at Week 64 and it was considered that the steady-state serum concentrations of ustekinumab were achieved by Week 28.

Foreign clinical studies

4.(i).A.(1).3) Single intravenous administration study (5.3.3.2.2, Study C0379T01 [April 2001 to August 2002])

An open-label, single ascending dose study was conducted in foreign patients with psoriasis vulgaris (n = 18, 92.98 ± 23.71 kg). The pharmacokinetic parameters following single ascending intravenous administrations of 0.09, 0.27, 0.9, and 4.5 mg/kg of ustekinumab were as shown in Table 9. C_{max} was reached immediately after intravenous infusion and then ustekinumab was eliminated biphasically until Week 16. The C_{max} and AUC_{∞} were dose-proportional over the dose range studied and the CL and Vd_z were constant, regardless of dose. The Vd_z was similar to the blood volume.

Table 9. Pharmacokinetic parameters following a single intravenous administration of ustekinumab to foreign patients with psoriasis vulgaris

Dose	C_{max} (μg/mL)	AUC_{∞} (μg.day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	Vd_z (mL/kg)
0.09 mg/kg	2.7 ± 0.5	48.2 ± 8.0	27.0 ± 7.5	1.90 ± 0.28	74.5 ± 24.1
0.27 mg/kg	8.9 ± 1.6	127.6 ± 14.3	18.5 ± 3.6	2.14 ± 0.26	56.1 ± 6.5
0.9 mg/kg	25.5 ± 7.2	434.7 ± 133.3	25.9 ± 3.7	2.22 ± 0.63	82.1 ± 23.6
4.5 mg/kg	136.8 ± 17.2	2346.8 ± 359.0	23.7 ± 5.7	1.96 ± 0.34	66.2 ± 15.4

Mean ± SD

[5] Data through Week 64 from subjects subcutaneously treated with ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 58-64 subjects; 90 mg group, 53-62 subjects; the placebo group was not included.)

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4.(i).A.(1).4) Single subcutaneous administration study (5.3.3.2.3, Study C0379T02 [June 2002 to May 2003])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with psoriasis vulgaris (n = 21, 96.4 ± 14.0 kg). The pharmacokinetic parameters following a single subcutaneous administration of 0.27, 0.675, 1.35, or 2.7 mg/kg of ustekinumab were as shown in Table 10. The C_{max} and AUC_{∞} increased in an almost dose-proportional manner over the dose range studied. The $t_{1/2}$ slightly increased dose-dependently though an adequate assessment was difficult for the low-dose group. The absolute bioavailability calculated from AUC_{∞} values after intravenous (Study T01) and subcutaneous (Study T02) administration was approximately 57.2%.

Table 10. Pharmacokinetic parameters following a single subcutaneous administration of ustekinumab to foreign patients with psoriasis vulgaris

Dose	C_{max} (μg/mL)	AUC_{∞} (μg.day/mL)	t_{max} (day)	$t_{1/2}$ (day)	F* (%)	CL/F (mL/day/kg)	Vz/F (mL/kg)
0.27 mg/kg	3.08 ± 1.70	90.8 ± 35.8	14.2 (7.1-15.1)	14.9 ± 4.6	67.9 ± 26.6	3.43 ± 1.65	72.8 ± 34.2
0.675 mg/kg	5.22 ± 2.58	169.7 ± 39.4	14.0 (4.0-14.3)	17.3 ± 2.5	49.3 ± 11.1	4.20 ± 0.95	106.1 ± 34.9
1.35 mg/kg	7.21 ± 2.39	323.1 ± 86.7	10.7 (7.0-14.2)	21.2 ± 3.6	47.9 ± 12.6	4.34 ± 0.95	131.1 ± 29.2
2.7 mg/kg	14.10 ± 2.82	832.3 ± 390.0	14.0 (7.1-14.1)	28.6 ± 9.3	61.4 ± 28.8	4.17 ± 2.75	144.4 ± 33.7

Mean ± SD, Median (Min-Max) for t_{max} *: Calculated as the ratio of AUC_{∞} after subcutaneous administration (Study T02) to AUC_{∞} after intravenous administration (Study T01)

4.(i).A.(1).5) Single or multiple subcutaneous administration study (5.3.5.1.1, Study C0379T04 [June 2003 to March 2005])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 320, 93.0 ± 22.7 kg). The pharmacokinetic parameters following a single subcutaneous administration or 4 weekly subcutaneous administrations of 45 or 90 mg of ustekinumab were as shown in Table 11 (Pharmacokinetic analysis population, 110 subjects). The $t_{1/2}$ following 4 weekly administrations of ustekinumab was similar to that following a single subcutaneous administration of ustekinumab.

Table 11. Pharmacokinetic parameters following a single subcutaneous administration or 4 weekly subcutaneous administrations of ustekinumab to foreign patients with psoriasis vulgaris

Dose		C_{max} (μg/mL)	AUC_{∞} (μg.day/mL)	t_{max} (day)	$t_{1/2}$ (day)
Single dose	45 mg	2.7 ± 1.2	196.7 ± 298.2	13.5 (1.9-58.2)	45.6 ± 80.2
	90 mg	6.1 ± 3.6	274.9 ± 206.5	7.0 (2.9-27.1)	26.7 ± 19.3
Multiple doses	45 mg	13.6 ± 5.7	-	3.0 (0.9-35.0)	24.9 ± 7.9
	90 mg	22.9 ± 13.1	-	3.0 (0.9-14.0)	28.1 ± 7.3

Mean ± SD, Median (Min-Max) for t_{max}

4.(i).A.(1).6) Multiple subcutaneous administration study (5.3.5.1.3-1 to 5.3.5.1.3-3, Study C0743T08 [December 2005 to ongoing (data cut-off of March 2009)])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 766, 93.88 ± 23.69 kg), to whom 45 or 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks. At each sampling timepoint from Week 4 through Week 28, serum ustekinumab concentrations were almost dose-proportional and the trough serum concentrations of ustekinumab (median)[6] in the 45 and 90 mg

[6] Data through Week 28 were obtained from subjects subcutaneously administered ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 242-253 subjects; 90 mg group, 236-253 subjects; the placebo group was not included.). Data at and after Week 52 were obtained from subjects who were re-randomized to receive dosing every 12 weeks at Week 40 (45 mg group, 52-75 subjects; 90 mg group,

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groups were 0.25 and 0.49 μg/mL, respectively, at Week 16; 0.21 and 0.47 μg/mL, respectively, at Week 28; 0.26 and 0.58 μg/mL, respectively, at Week 52; 0.50 and 0.89 μg/mL, respectively, at Week 88; 0.49 and 0.88 μg/mL, respectively, at Week 112; and 0.44 and 1.08 μg/mL, respectively, at Week 148.

4.(i).A.(1).7) Multiple subcutaneous administration study (5.3.5.1.4-1 to 5.3.5.1.4-3, Study C0743T09 [March 2006 to ongoing (data cut-off of August 2008)])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in foreign patients with plaque psoriasis (n = 1230, 90.99 ± 21.28 kg). When 45 or 90 mg of ustekinumab were subcutaneously administered at Weeks 0 and 4 and then every 12 weeks, serum ustekinumab concentrations were dose-proportional and the trough serum concentrations of ustekinumab (median)[7] in the 45 and 90 mg groups were 0.37 and 0.65 μg/mL, respectively, at Week 16; 0.34 and 0.56 μg/mL, respectively, at Week 28; 0.36 and 0.64 μg/mL, respectively, at Week 40; and 0.40 and 0.68 μg/mL, respectively, at Week 52. The steady-state serum concentrations of ustekinumab were considered to be achieved by Week 28. When 45 or 90 mg of ustekinumab were subcutaneously administered every 8 weeks beginning at Week 28, the trough serum concentrations of ustekinumab (median) at Week 52 were 3.4-fold and 2.5-fold higher, respectively, than those following dosing every 12 weeks. The liquid in vial formulation (LIV formulation) was switched to the liquid in prefilled syringe formulation (PFS formulation) at Week 52 for a long-term extension period and the trough serum concentrations of ustekinumab (median)[8] after administration of 45 and 90 mg of ustekinumab every 12 weeks were similar between the two formulations, i.e. 0.38 and 0.68 μg/mL, respectively, at Week 40 and 0.40 and 0.72 μg/mL, respectively, at Week 52 for the LIV formulation and 0.42 and 0.73 μg/mL, respectively, at Week 88 for the PFS formulation.

4.(i).A.(2) Population pharmacokinetic analysis

4.(i).A.(2).1) Population pharmacokinetic (PPK) analysis using the data from clinical studies in foreign patients with psoriasis (5.3.3.5.1)

Using the serum ustekinumab concentration data from a total of 1937 subjects (9938 sampling points) in phase III studies in foreign patients with psoriasis (Studies T08 and T09), PPK analysis was performed using non-linear mixed effect modeling (NONMEM). A one-compartment model with first-order absorption was used as a base model to build up a final model. The CL/F and Vd/F values for ustekinumab estimated from the final model were 0.465 L/day and 15.7 L, respectively. Factors that could contribute to the variability in CL/F and Vd/F were identified. Body weight, diabetes comorbidity, positive immune response to ustekinumab, albumin, creatinine clearance, gender, and

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59-84 subjects). The applicant explained that at and after Week 88, higher values were obtained because the assay method was changed from ECLIA-BV to ECLIA-MSD.

[7] Data from subjects subcutaneously administered ustekinumab at Weeks 0 and 4 and then every 12 weeks (45 mg group, 243-249 subjects; 90 mg group, 279-285 subjects). Subjects in the placebo group or subjects who failed to achieve a PASI 75 response or who were adjusted to dosing every 8 weeks at Week 28 were not included.

[8] Data from subjects who achieved a PASI 75 response at Weeks 28 and 40 and continued dosing every 12 weeks and received the PFS formulation during the long-term extension period after Week 52 (45 mg group, 206-211 subjects; 90 mg group, 260-272 subjects). Note that subjects who received placebo at Weeks 0 and 4 were included.

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alkaline phosphatase were selected as statistically significant ($P < 0.005$) covariates on CL/F and body weight, race, and diabetes co-morbidity were selected as statistically significant covariates on Vd/F. Of these covariates, the inter-subject variability due to body weight, diabetes co-morbidity, or positive immune response to ustekinumab was ≥20%.

The final model-predicted CL/F and Vd/F values (0.68 L/day and 19.5 L, respectively [median]) were approximately 55% and 37% higher, respectively, in subjects weighing >100 kg compared to subjects weighing ≤100 kg (0.44 L/day and 14.2 L, respectively [median]) and the estimated steady-state trough serum concentration of ustekinumab was approximately 30% lower in subjects weighing >100 kg compared to subjects weighing ≤100 kg.

The final model-predicted CL/F and Vd/F values were approximately 28.7% and 13.2% higher, respectively, in subjects with diabetes co-morbidity compared to subjects without diabetes and the estimated trough serum ustekinumab concentration and the estimated AUC_∞ value were approximately 20% lower in subjects with diabetes compared to those without diabetes. Moreover, the trough serum ustekinumab concentration and AUC_∞ value were approximately 40% to 50% lower in subjects with diabetes weighing >100 kg compared to those without diabetes weighing ≤100 kg.

Although the incidence of anti-ustekinumab antibody positive subjects was as low as approximately 5%, the final model-predicted CL/F value was 35.5% higher in subjects positive for anti-ustekinumab antibodies compared to antibody-negative subjects (including inconclusive subjects).

The final model-predicted CL/F value was 5.9% higher in women compared to men and the Vd/F value was 11.1% higher in non-white subjects compared to white subjects. It was considered that the effects of the renal function (creatinine clearance) and hepatic function (albumin and alkaline phosphatase) on the pharmacokinetics of ustekinumab are also small, though assessed in a limited fashion. The potential impact of 28 concomitant medications most frequently used by subjects on the CL/F of ustekinumab were evaluated in the PPK analysis and none of the concomitant medications had a significant effect.

4.(i).A.(3) Comparison of pharmacokinetics of ustekinumab between Japanese and foreign patients (5.3.3.3.1, 5.3.3.5.2)

Using the data from Japanese Study JPN-01 and Foreign Study T04, the pharmacokinetics of a single subcutaneous dose of ustekinumab were compared. The median C_{max} and AUC_∞ were 1.07- to 1.81-fold higher in Japanese patients with psoriasis compared to foreign patients and as body weight of foreign patients with psoriasis (median body weight, 89.0 kg) was 1.34-fold heavier than body weight of Japanese patients with psoriasis (median body weight, 66.20 kg), it was discussed that the pharmacokinetic differences between Japanese and foreign patients were potentially due to the effect of body weight. Using the data from Japanese Study JPN-02 and Foreign Studies T08 and T09, the pharmacokinetics of multiple subcutaneous doses of ustekinumab were also compared. The trough

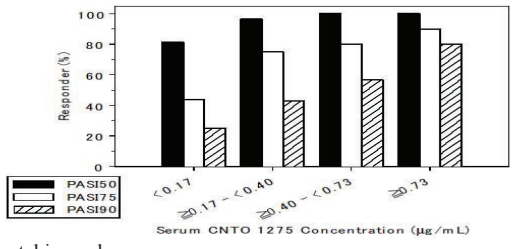
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serum concentrations of ustekinumab (median) at Week 28 were 0.25 μg/mL in the 45 mg group and 0.65 μg/mL in the 90 mg group in Japanese patients, which were 0.96- to 1.19-fold and 1.33- to 1.38-fold higher, respectively, than those in foreign patients (0.21-0.26 and 0.47-0.49 μg/mL, respectively). Based on comparison of serum ustekinumab concentrations among subjects stratified by body weight (≤70 kg or >70 kg; ≤100 kg or >100 kg), it was discussed that these differences were also due to differences in body weight.

Furthermore, as covariates in the final model obtained from the PPK analysis of phase III studies in foreign patients with psoriasis (Studies T08 and T09), the subject background data from Japanese Study JPN-02 were used to predict the serum ustekinumab concentration over time in Japanese patients with psoriasis. As a result, although the observed concentrations at Weeks 2 and 20 fell outside of the 5-to-95 percentile range of the predicted values, it was explained that the pharmacokinetic differences between Japanese and foreign patients were due to the confounding effect of body weight, as the predicted values almost agreed with the observed values.

4.(i).A.(4) Correlation between serum ustekinumab concentration and efficacy in psoriasis patients (5.3.5.1.2-1, 5.3.5.3.1)

In Japanese Study JPN-02, the proportions of subjects who achieved Psoriasis Area and Severity Index[9] (PASI) 50, 75, and 90 responses (PASI 50, PASI 75, and PASI 90 response rates, respectively) at Week 28 by serum ustekinumab (trough) concentrations following multiple subcutaneous administrations of 45 mg or 90 mg of ustekinumab were as shown in Figure 1. The PASI 75 and PASI 90 response rates increased with increasing serum ustekinumab concentrations. Foreign Studies T08 and T09 also showed a similar trend. According to subgroup analyses of responders, partial responders and nonresponders (subjects who achieved a ≥75%, ≥50% and <75%, and <50% improvement in PASI score from baseline, respectively) at Week 28 in each of Studies JPN-02, T08, and T09, the serum ustekinumab (trough) concentration (median) was higher in this order.



Serum ustekinumab concentration (μg/mL)	<0.17	≥0.17 - <0.40	≥0.40 - <0.73	≥0.73
n	32	28	30	30

Figure 1. PASI 50, 75, and 90 response rates by serum ustekinumab concentrations; Week 28 (Study JPN-02)

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Racial differences in pharmacokinetic (PK)/pharmacodynamic (PD) profile

It was explained that higher serum ustekinumab concentrations in Japanese patients compared to foreign patients were due to lower body weight of Japanese patients compared to foreign patients.

[9] The body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for erythema, infiltration/induration, and scaling, which are each rated on a 5-point scale and for area of involvement. For each of the four body areas, the three symptom scores are added and then multiplied by the area score. Each body region's score is then multiplied by the proportions to reflect its contribution to total body area (10% for head, 20% for upper extremities, 30% for trunk, 40% for lower extremities). The scores for all four body areas are added to yield the overall PASI score (Scores range from 0 to 72.0).

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Meanwhile, the trough concentration was higher, but the PASI 75 response rate tended to be lower in Japanese patients compared to foreign patients. PMDA asked the applicant to discuss racial differences in the pharmacokinetic (PK)/pharmacodynamic (PD) profile of ustekinumab.

The applicant explained as follows:
Since BSA involvement and PASI score at baseline were higher in Japanese patients with psoriasis (Study JPN-02) compared to foreign patients with psoriasis (Studies T08 and T09), the applicant considered that the severity of psoriasis at baseline may affect the pharmacokinetics and efficacy of ustekinumab. Thus, baseline PASI, Physician's Global Assessment (PGA), and Dermatology Life Quality Index scores related to severity and disease duration (years) were evaluated as potential covariates in the PPK and PPK/PD analyses of the data from Studies T08 and T09. As a result, none of them were statistically significant covariates. Also when the effects of the severity of psoriasis at baseline and disease duration (years) on the PASI response rate were evaluated by subgroup analyses of Studies JPN-02 and T08 and T09, there was no clear correlation between these factors and efficacy and moreover, no effects of other patient background factors on efficacy were suggested.

PMDA concluded that although the cause for differences in the PK/PD profile between Japanese and foreign patients is not clear, ustekinumab is generally highly effective in treating skin symptoms and these differences are not clinically relevant.

4.(i).B.(2) Pharmacokinetics and clinical response in patients with diabetes co-morbidity
Foreign Studies T08 and T09 showed a trend toward lower trough concentrations and reduced efficacy in patients with diabetes compared to those without diabetes and body weight and diabetes co-morbidity were selected as covariates on CL/F and Vd/F in the PPK analysis. PMDA asked the applicant to discuss its cause and explain whether dose adjustment is required for patients with diabetes co-morbidity.

The applicant explained as follows:
The trough serum concentration of ustekinumab estimated from the final model obtained in the PPK analysis of Studies T08 and T09 was approximately 20% lower in subjects with diabetes compared to subjects without diabetes of the same body weight and according to the pooled data from Studies T08 and T09, the PASI 75 response rate was slightly lower in subjects with diabetes than in subjects without diabetes in both subgroups of subjects weighing ≤100 kg or >100 kg. Thus, it is considered that lower serum ustekinumab concentrations and reduced efficacy in patients with diabetes are due to the effects of not only body weight but also diabetes itself, which may be attributable to altered vascular permeability and lymph distribution of drugs in patients with diabetes. On the other hand, in order to determine the effect of the severity of diabetes, the relationship between baseline HbA1c and trough serum concentration of ustekinumab/percent improvement in PASI score in Studies T08 and T09 was examined. As a result, there was a statistically significant but weak negative correlation between baseline HbA1c and both trough serum concentration of ustekinumab and percent

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improvement in PASI score. Thus, no specific dose adjustment is required for patients with diabetes co-morbidity.

PMDA accepts the above response at present, but considers that as the number of subjects with high HbA1c was limited in the clinical studies, the efficacy of ustekinumab in patients with diabetes co-morbidity needs to be further investigated, including the effect of the severity of diabetes, via post-marketing surveillance.

4.(i).B.(3) Anti-ustekinumab antibodies

The applicant explained the incidence of anti-ustekinumab antibody production and its relationship with the pharmacokinetics and efficacy of ustekinumab, etc. as follows:

The incidences of anti-ustekinumab antibody positive subjects in Japanese Study JPN-02 and Foreign Studies T04, T08, and T09 were 6.5% (10 of 153 subjects) [through Week 72], 4.1% (12 of 293 subjects) [through Week 52], 5.1% (38 of 746 subjects) [through Week 76], and 5.3% (64 of 1202 subjects) [through Week 88], respectively, and no differences between Japanese and foreign patients with psoriasis were observed. Japanese Study JPN-02 showed that the incidence of anti-ustekinumab antibody positive subjects tended to be higher in the 45 mg group (9.4%, 6 of 64 subjects) than in the 90 mg group (3.3%, 2 of 61 subjects) and a similar trend was observed also in foreign patients with psoriasis. When stratified by body weight, the incidence of anti-ustekinumab antibody positive subjects was lower in subjects weighing ≤100 kg (3.6%, 48 of 1341 subjects) than in subjects weighing >100 kg (9.1%, 55 of 606 subjects) in Studies T08 and T09. Anti-ustekinumab antibodies were detected by around Week 28 in Study JPN-02 and by around Week 52 in Studies T08 and T09 and 4.4% (13 of 297 subjects) of subjects who were retreated with ustekinumab after withdrawal from ustekinumab therapy developed anti-ustekinumab antibodies, which was similar to the incidence in the overall study population.

In Studies T02, T04, and T08, samples from 50 of 51 subjects positive for anti-ustekinumab antibodies were assessed for ustekinumab neutralizing potential and 29 (58.0%) of the 50 subjects were positive for neutralizing antibodies that are able to neutralize the pharmacological activity of ustekinumab. Some of the anti-ustekinumab antibody positive subjects were not positive for neutralizing antibodies. They had low antibody titers and probably, the neutralizing effect of antibodies could not be detected.

Following multiple subcutaneous administrations of ustekinumab to Japanese and foreign patients with psoriasis, anti-ustekinumab antibody positive subjects tended to have lower serum ustekinumab concentrations (median) than antibody negative subjects.

The PASI 75 and PASI 90 response rates at Week 28 tended to be lower in anti-ustekinumab antibody positive subjects compared to antibody negative subjects in Japanese Study JPN-02 and a similar trend was observed also in foreign studies. However, since many antibody-positive subjects achieved a

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PASI 50 response and some achieved a PASI 75 response, it was discussed that anti-ustekinumab antibody development has no significant impact on clinical response.

PMDA considers as follows:
Based on the above, no clinically relevant problems with anti-ustekinumab antibody development have been suggested at present. Meanwhile, the relationship between neutralizing activity of antibodies and the efficacy and pharmacokinetics of ustekinumab has not adequately been examined and the proportion of antibody positive subjects who were positive for neutralizing antibodies tended to be relatively high (≥50%). Taking account of these points, a further investigation on antibodies and their neutralizing activity etc. in patients with markedly reduced efficacy during continued treatment is necessary.

4.(ii) Summary of clinical efficacy and safety

4.(ii).A Summary of the submitted data

As the efficacy and safety evaluation data, the results from a phase I study (Study JNS009-JPN-01 [5.3.3.2.1]) and a phase II/III study (Study JNS009-JPN-02 [5.3.5.1.2-1 to 5.3.5.1.2-2]) in Japanese patients with psoriasis and a phase I single intravenous administration study (Study C0379T01 [5.3.3.2.2]), a phase I single subcutaneous administration study (Study C0379T02 [5.3.3.2.3]), a phase II study (Study C0379T04 [5.3.5.1.1]), a phase II study (Study C0743T10 [5.3.5.4.1]), a phase III study (Study C0743T08 [5.3.5.1.3-1 to 5.3.5.1.3-3]), and a phase III study (Study C0743T09 [5.3.5.1.4-1 to 5.3.5.1.4-3]) in foreign patients with psoriasis were submitted.

4.(ii).A.(1) Studies in Japanese patients

4.(ii).A.(1).1) Phase I study (5.3.3.2.1, JNS009-JPN-01 [February 2006 to March 2007])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in patients with psoriasis vulgaris (Target sample size of 24 subjects [6 subjects each in the ustekinumab 22.5 mg, 45 mg, and 90 mg and placebo groups]) to evaluate the efficacy, safety, and pharmacokinetics of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

A single subcutaneous dose of 22.5 mg of ustekinumab (6 subjects) or placebo (2 subjects) was to be administered in STEP1, a single subcutaneous dose of 45 mg of ustekinumab (6 subjects) or placebo (2 subjects) in STEP2, and a single subcutaneous dose of 90 mg of ustekinumab (6 subjects) or placebo (2 subjects) in STEP3. After safety was confirmed in each STEP, the study was to move to the next STEP. Subjects were followed through Week 24.

All of the 24 subjects treated were included in the Full Analysis Set (FAS), which was used as the safety population, and 23 subjects (6 subjects in the 22.5 mg group, 6 subjects in the 45 mg group, 6 subjects in the 90 mg group, 5 subjects in the placebo group), excluding 1 subject in the placebo group

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who received rescue medication due to exacerbation of the primary disease, were included in the Per Protocol Set, which was used as the primary efficacy population.

The Psoriasis Area and Severity Index[10] (PASI) 75 response rate[11] at Week 12 was an efficacy endpoint. The PASI 75 response rates at Week 12 were 33.3% (2 of 6 subjects) in the 22.5 mg group, 100% (6 of 6 subjects) in the 45 mg group, 75% (3 of 4 subjects) in the 90 mg group, and 0% in the placebo group, and the ustekinumab groups showed greater improvement compared to the placebo group.

Adverse events (including abnormal laboratory test values) occurred in all subjects (24 of 24 subjects). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Adverse drug reactions[12] occurred in all subjects (24 of 24 subjects) and those reported by ≥2 subjects in any of the ustekinumab groups were nasopharyngitis [33.3% (2 of 6 subjects) in the 22.5 mg group, 16.7% (1 of 6 subjects) in the 45 mg group, 33.3% (2 of 6 subjects) in the 90 mg group, 0% (0 of 6 subjects) in the placebo group], activated partial thromboplastin time prolonged [50.0% (3 of 6 subjects) in the 22.5 mg group, 33.3% (2 of 6 subjects) in the 45 mg group, 33.3% (2 of 6 subjects) in the 90 mg group, 0% (0 of 6 subjects) in the placebo group], and B-lymphocyte count decreased [33.3% (2 of 6 subjects) in the 22.5 mg group, 50.0% (3 of 6 subjects) in the 45 mg group, 16.7% (1 of 6 subjects) in the 90 mg group, 66.7% (4 of 6 subjects) in the placebo group].

4.(ii).A.(1).2) Phase II/III study (5.3.5.1.2-1 to 5.3.5.1.2-2, JNS009-JPN-02 [March 2008 to March 2010])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in Japanese patients with moderate to severe[13] plaque psoriasis (psoriasis vulgaris, psoriatic arthritis) (Target sample size of 150 [60 subjects per active treatment group, 30 subjects in the placebo group]) to evaluate the efficacy and safety of ustekinumab.

Ustekinumab 45 or 90 mg or placebo was to be subcutaneously administered according to Table 12. Subjects were followed for efficacy and safety through Week 64 and Week 72, respectively.

When the pharmacokinetics of ustekinumab were compared between Japanese Study JPN-01 and Foreign Study T04, the pharmacokinetics of ustekinumab were considered similar between Japanese

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[10] The body is divided into 4 regions: the head, upper extremities, trunk, and lower extremities. Each of these areas is assessed separately for erythema, infiltration/induration, and scaling, which are each rated on a 5-point scale and for area of involvement. For each of the four body areas, the three symptom scores are added and then multiplied by the area score. Each body region's score is then multiplied by the proportions to reflect its contribution to total body area (10% for head, 20% for upper extremities, 30% for trunk, 40% for lower extremities). The scores for all four body areas are added to yield the overall PASI score (Scores range from 0 to 72.0).

[11] The proportion of subjects who achieved a ≥75% reduction in PASI score from baseline.

[12] Adverse events for which a causal relationship to study drug could not be denied (adverse events other than those assessed as "unrelated to" study drug).

[13] Body surface area (BSA) involvement of ≥10% and PASI score of ≥12.

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and foreign patients of the same body weight range [see "4.(i) Summary of clinical pharmacology studies"] and 9 of 10 patients who received 45 or 90 mg of ustekinumab achieved a PASI 75 response in Study JPN-01. Thus, for this study, the same dosing regimen as that for foreign phase III studies (Studies T08 and T09) was selected.

Table 12. Ustekinumab dosing schedule for each treatment group

	Week 0	Week 4	Week 12	Week 16	Every 12 weeks after Week 28 through Week 52
45 mg group	45 mg	45 mg	Placebo	45 mg	45 mg
90 mg group	90 mg	90 mg	Placebo	90 mg	90 mg
Placebo→45 mg group	Placebo	Placebo	45 mg	45 mg	45 mg
Placebo→90 mg group	Placebo	Placebo	90 mg	90 mg	90 mg

All of the 158 subjects treated (64 subjects in the 45 mg group, 62 subjects in the 90 mg group, 32 subjects in the placebo group) were included in the safety population and 157 subjects (64 subjects in the 45 mg group, 62 subjects in the 90 mg group, 15 subjects in the placebo→45 mg group, 16 subjects in the placebo→90 mg group), excluding 1 subject for whom an emergency code break was required before efficacy data collection, were included in the FAS, which was used as the primary efficacy population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 was 59.4% (38 of 64 subjects) in the 45 mg group, 67.7% (42 of 62 subjects) in the 90 mg group, and 6.5% (2 of 31 subjects) in the placebo group, as shown in Table 13, and the differences between both of the ustekinumab groups and the placebo group were statistically significant ($P < 0.0001$ for both [Fisher's exact test], using Holm's method). The secondary endpoints of the PASI 50 response rate and the PASI 90 response rate were as shown in Table 13.

Table 13. PASI response rate at Week 12

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
PASI 50 response rate	12.9 (4/31)	82.8 (53/64)	83.9 (52/62)
PASI 75 response rate	6.5 (2/31)	59.4 (38/64)	67.7 (42/62)
PASI 90 response rate	3.2 (1/31)	32.8 (21/64)	43.5 (27/62)

% (n)

Of the 157 patients, 22 patients had joint symptoms and among these patients, the PASI 75 response rates at Week 12 were 83.3% (5 of 6 subjects) in the 45 mg group, 46.2% (6 of 13 subjects) in the 90 mg group, and 0% (0 of 3 subjects) in the placebo group.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 65.6% (42 of 64 subjects) (85 events) in the 45 mg group, 59.7% (37 of 62 subjects) (80 events) in the 90 mg group, and 65.6% (21 of 32 subjects) (38 events) in the placebo group. No deaths were reported. The incidences of serious adverse events were 4.8% (3 of 62 subjects) (4 events) (pneumonia; prostate cancer; and psoriasis and osteonecrosis, 1 subject each) in the 90 mg group and 6.3% (2 of 32 subjects) (3 events) (cardiac failure congestive [1 subject], psoriasis and dermatitis exfoliative [1 subject]) in the placebo group, and although a causal relationship to study drug could not

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be denied for pneumonia, prostate cancer, and psoriasis in the 90 mg group and cardiac failure congestive in the placebo group, the outcomes of all events were reported as resolved or improved. The incidences of adverse events leading to treatment discontinuation were 6.5% (4 of 62 subjects) (4 events) (psoriasis [2 subjects], pneumonia [1 subject], prostate cancer [1 subject]) in the 90 mg group and 6.3% (2 of 32 subjects) (3 events) (psoriasis [1 subject], psoriasis and dermatitis exfoliative [1 subject]) in the placebo group, and a causal relationship to study drug could not be denied for pneumonia, prostate cancer, and psoriasis (2 subjects) in the 90 mg group and the outcomes of all events were reported as resolved or improved.

The incidences of adverse drug reactions were 54.7% (35 of 64 subjects) (59 events) in the 45 mg group, 45.2% (28 of 62 subjects) (53 events) in the 90 mg group, and 59.4% (19 of 32 subjects) (30 events) in the placebo group and those reported by ≥2 subjects in any group were as shown in Table 14.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 72[14] were 96.9% (62 of 64 subjects) (447 events) in the 45 mg group, 98.4% (61 of 62 subjects) (417 events) in the 90 mg group, 93.3% (14 of 15 subjects) (89 events) in the placebo→45 mg group, and 100% (13 of 13 subjects) (69 events) in the placebo→90 mg group. No deaths were reported. The incidences of serious adverse events were 7.8% (5 of 64 subjects) (7 events) in the 45 mg group, 9.7% (6 of 62 subjects) (9 events) in the 90 mg group, 6.7% (1 of 15 subjects) (1 event) in the placebo→45 mg group, and 7.7% (1 of 13 subjects) (1 event) in the placebo→90 mg group. Those occurring after Week 12 were as follows: 45 mg group (fall; cellulitis; cervix carcinoma stage 0; cataract; and pharyngitis, colonic polyp, and diabetes mellitus, 1 subject each), 90 mg group (dislocation of the prosthetic femoral head; fall; cerebral haemorrhage; and cataract, 1 subject each), placebo→45 mg group (lumbar spinal stenosis [1 subject]), and placebo→90 mg group (electrocardiogram abnormal [1 subject]). Although a causal relationship to study drug could not be denied for pharyngitis, colonic polyp, and cellulitis in the 45 mg group, cerebral haemorrhage and cataract in the 90 mg group, and lumbar spinal stenosis in the placebo→45 mg group, the outcomes of all events were reported as resolved or improved, except that the outcome of cerebral haemorrhage (1 subject in the 90 mg group) was reported as improved with sequelae.

The incidences of adverse events leading to treatment discontinuation after Week 12 were 1.6% (1 of 64 subjects) (1 event) (cervix carcinoma stage 0) in the 45 mg group, 1.6% (1 of 62 subjects) (1 event) (cerebral haemorrhage) in the 90 mg group, and 7.7% (1 of 13 subjects) (1 event) (hepatic steatosis) in the placebo→90 mg group. Although the 1 subject discontinued treatment due to hepatic steatosis after Week 12, hepatic steatosis occurred during the placebo administration period before Week 12.

[14] From Week 12 through Week 72, after crossover to ustekinumab.

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The incidences of adverse drug reactions were 87.5% (56 of 64 subjects) (304 events) in the 45 mg group, 87.1% (54 of 62 subjects) (300 events) in the 90 mg group, 93.3% (14 of 15 subjects) (74 events) in the placebo→45 mg group, and 92.3% (12 of 13 subjects) (42 events) in the placebo→90 mg group. Adverse drug reactions reported by ≥2 subjects in any group were as shown in Table 15.

Table 14. Adverse drug reactions reported by ≥2 subjects in any group (through Week 12)

Preferred terms	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
Nasopharyngitis	2 (6.3)	9 (14.1)	8 (12.9)
Folliculitis	0	1 (1.6)	2 (3.2)
Psoriasis	5 (15.6)	1 (1.6)	3 (4.8)
Eczema	0	1 (1.6)	2 (3.2)
Arthralgia	0	3 (4.7)	0
Blood triglycerides increased	1 (3.1)	4 (6.3)	0
Eosinophil count increased	1 (3.1)	2 (3.1)	3 (4.8)
Basophil count increased	0	2 (3.1)	2 (3.2)
Blood uric acid increased	0	1 (1.6)	2 (3.2)
Lymphocyte count decreased	0	2 (3.1)	0

n (%)

Table 15. Adverse drug reactions reported by ≥2 subjects in any group (through Week 72)

Preferred terms	Placebo→45 mg	Placebo→90 mg	45 mg	90 mg
Nasopharyngitis	7 (46.7)	7 (53.8)	27 (42.2)	26 (41.9)
Influenza	0	0	2 (3.1)	5 (8.1)
Folliculitis	2 (13.3)	0	2 (3.1)	4 (6.5)
Cystitis	0	0	2 (3.1)	0
Skin papilloma	0	0	0	3 (4.8)
Seasonal allergy	1 (6.7)	0	2 (3.1)	5 (8.1)
Hyperlipidaemia	1 (6.7)	0	3 (4.7)	0
Headache	0	1 (7.7)	5 (7.8)	1 (1.6)
Conjunctivitis	0	0	2 (3.1)	1 (1.6)
Ventricular extrasystoles	0	0	2 (3.1)	2 (3.2)
Hypertension	0	0	2 (3.1)	4 (6.5)
Rhinitis allergic	1 (6.7)	0	1 (1.6)	4 (6.5)
Oropharyngeal pain	0	1 (7.7)	0	2 (3.2)
Dental caries	0	0	3 (4.7)	3 (4.8)
Diarrhoea	0	1 (7.7)	4 (6.3)	0
Periodontal disease	1 (6.7)	0	0	2 (3.2)
Enterocolitis	0	0	2 (3.1)	0
Hepatic function abnormal	0	0	3 (4.7)	3 (4.8)
Eczema	1 (6.7)	0	2 (3.1)	3 (4.8)
Psoriasis	0	0	3 (4.7)	4 (6.5)
Urticaria	1 (6.7)	1 (7.7)	1 (1.6)	2 (3.2)
Acne	0	1 (7.7)	0	3 (4.8)
Xeroderma	1 (6.7)	0	2 (3.1)	2 (3.2)
Heat rash	0	0	2 (3.1)	0
Pruritus	0	0	2 (3.1)	0
Back pain	1 (6.7)	0	1 (1.6)	2 (3.2)
Arthralgia	0	1 (7.7)	6 (9.4)	1 (1.6)
Pain in extremity	0	0	2 (3.1)	0
Pyrexia	1 (6.7)	1 (7.7)	2 (3.1)	0
Blood triglycerides increased	2 (13.3)	1 (7.7)	10 (15.6)	8 (12.9)
Blood creatine phosphokinase increased	2 (13.3)	2 (15.4)	7 (10.9)	9 (14.5)
Alanine aminotransferase increased	2 (13.3)	2 (15.4)	4 (6.3)	6 (9.7)
Eosinophil count increased	0	0	4 (6.3)	6 (9.7)
White blood cell count increased	0	1 (7.7)	4 (6.3)	4 (6.5)
Blood lactate dehydrogenase increased	1 (6.7)	0	5 (7.8)	3 (4.8)
Lymphocyte count decreased	1 (6.7)	0	5 (7.8)	1 (1.6)
Basophil count increased	0	0	3 (4.7)	4 (6.5)
Glucose urine present	1 (6.7)	0	2 (3.1)	3 (4.8)
Blood cholesterol increased	1 (6.7)	0	3 (4.7)	0
Blood amylase increased	0	1 (7.7)	1 (1.6)	2 (3.2)
Blood bilirubin increased	0	1 (7.7)	2 (3.1)	1 (1.6)
C-reactive protein increased	1 (6.7)	0	1 (1.6)	3 (4.8)

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Protein urine present	0	0	0	3 (4.8)
Blood creatinine increased	0	0	0	2 (3.2)
Blood uric acid increased	0	0	1 (1.6)	2 (3.2)
Liver function test abnormal	0	0	0	3 (4.8)
Red blood cell count increased	1 (6.7)	0	0	2 (3.2)
White blood cell count decreased	0	0	2 (3.1)	1 (1.6)
Blood phosphorus decreased	1 (6.7)	0	0	2 (3.2)
Blood phosphorus increased	0	0	2 (3.1)	0
Blood urea increased	0	0	0	2 (3.2)
Blood urine present	0	0	0	2 (3.2)
Weight increased	0	0	2 (3.1)	0

n(%)

Based on the above, the applicant explained as follows:

The efficacy of ustekinumab was confirmed. When the efficacy of ustekinumab at different dose levels was examined, the PASI 75 response rate at Week 12 was 8.3% higher in the 90 mg group compared to the 45 mg group while the PASI 50 response rate was almost the same in the 45 mg and 90 mg groups, which indicated that both dose levels of ustekinumab can achieve clinically significant improvement in skin lesions in most patients, etc. Thus, the recommended clinical dose of ustekinumab should be 45 mg. On the other hand, given that foreign studies showed that the trough serum concentration of ustekinumab and the PASI 75 response rate in the 90 mg group tended to be lower in subjects weighing >100 kg compared to those weighing ≤100 kg, etc., it was decided that a 90 mg dose may be used in patients weighing >100 kg.

4.(ii).A.(2) Studies in foreign patients

4.(ii).A.(2).1) Single intravenous administration study (5.3.3.2.2, C0379T01 [April 2001 to August 2002])

An open-label, uncontrolled study was conducted in patients with moderate to severe psoriasis vulgaris (Target sample size of 23 [4 subjects each in the 0.09 and 0.27 mg/kg groups, 5 subjects each in the 0.9, 4.5, and 18 mg/kg groups]) to evaluate the pharmacokinetics, efficacy, and safety of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

A single dose of 0.09, 0.27, 0.90, 4.5, or 18 mg/kg[15] of ustekinumab was to be administered as an intravenous infusion over ≥2 hours. Ustekinumab treatment was started with the lowest dose and after safety was confirmed, the dose was to be escalated to the next dose level. Subjects were followed through Week 16.

All of the 18 subjects treated[16] (4 subjects each in the 0.09 and 0.27 mg/kg groups, 5 subjects each in the 0.9 and 4.5 mg/kg groups) were included in the safety and efficacy populations.

The percent improvement in PASI score from baseline (mean ± SD) was an efficacy endpoint. The percent improvements in the 0.09, 0.27, 0.9, and 4.5 mg/kg groups were 68.5 ± 25.1%, 54.3 ± 49.1%,

[15] Although the study was intended to be conducted at doses of 0.1, 0.3, 1.0, 5.0, and 20 mg/kg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

[16] An 18 mg/kg group was not included in the study due to protocol amendments.

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73.6 ± 20.0%, and 97.1 ± 4.9%, respectively, at Week 12, and 58.1 ± 32.5%, 50.0 ± 45.0%, 80.4 ± 18.9%, and 94.9 ± 7.2%, respectively, at Week 16.

Adverse events (including abnormal laboratory test values) occurred in all subjects (18 of 18 subjects). No deaths were reported. A serious adverse event occurred in 1 subject in the 4.5 mg/kg group (herniated disk) and its causal relationship to study drug was denied. There were no adverse events leading to treatment discontinuation.

Adverse drug reactions occurred in all subjects except for 2 subjects in the 0.9 mg/kg group and 1 subject in the 4.5 mg/kg group. Those reported by ≥2 subjects in any group were lymphocyte count decreased (3 subjects in the 0.09 mg/kg group, 3 subjects in the 0.27 mg/kg group, 2 subjects in the 0.9 mg/kg group, 2 subjects in the 4.5 mg/kg group) and headache (1 subject in the 0.09 mg/kg group, 3 subjects in the 0.27 mg/kg group, 1 subject in the 0.9 mg/kg group, 1 subject in the 4.5 mg/kg group).

4.(ii).A.(2).2) Single subcutaneous administration study (5.3.3.2.3, C0379T02 [June 2002 to May 2003])

A placebo-controlled, double-blind, parallel-group, comparative study was conducted in patients with moderate to severe psoriasis vulgaris (Target sample size of 20 [4 subjects each in the ustekinumab 0.27, 0.675, 1.35, and 2.7 mg/kg and placebo groups]) to evaluate the pharmacokinetics, efficacy, and safety of ustekinumab [see "4.(i) Summary of clinical pharmacology studies" for pharmacokinetics].

In Cohort 1, a single subcutaneous dose of 0.27 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 2, a single subcutaneous dose of 0.675 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 3, a single subcutaneous dose of 1.35 mg/kg of ustekinumab (4 subjects) or placebo (1 subject) was to be administered. In Cohort 4, a single subcutaneous dose of 2.7 mg/kg of ustekinumab (4 subjects) or placebo (1 subject)[17] was to be administered. After safety was confirmed in each cohort, the next dose cohort was to be initiated. Subjects were followed through Week 24.

All of the 21 subjects treated (5 subjects in the 0.27 mg/kg group, 4 subjects each in the 0.675, 1.35, and 2.7 mg/kg and placebo groups) were included in the safety and efficacy populations.

The percent improvement in PASI score from baseline (mean ± SD) was an efficacy endpoint. The percent improvements in the 0.27, 0.675, 1.35, 2.7 mg/kg, and placebo groups were 53.1 ± 26.0%, 76.7 ± 13.3%, 57.3 ± 11.3%, 85.4 ± 8.0%, and 43.4 ± 27.4%, respectively, at Week 12 and 25.1 ± 32.8%, 33.2 ± 45.1%, 44.9 ± 27.5%, 76.5 ± 10.2%, and -5.0 ± 52.6%, respectively, at Week 24.

[17] Although the study was intended to be conducted at doses of 0.3, 0.75, 1.5, and 3.0 mg/kg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

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The incidences of adverse events (including abnormal laboratory test values) were 100% (5 of 5 subjects) in the 0.27 mg/kg group, 75% (3 of 4 subjects) in the 0.675 mg/kg group, 75% (3 of 4 subjects) in the 1.35 mg/kg group, 100% (4 of 4 subjects) in the 2.7 mg/kg group, and 100% (4 of 4 subjects) in the placebo group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

The incidences of adverse drug reactions were 100% (5 of 5 subjects) in the 0.27 mg/kg group, 75% (3 of 4 subjects) in the 0.675 mg/kg group, 50% (2 of 4 subjects) in the 1.35 mg/kg group, 100% (4 of 4 subjects) in the 2.7 mg/kg group, and 75% (3 of 4 subjects) in the placebo group, and those reported by ≥2 subjects in any group were blood creatine phosphokinase increased (3 subjects in the 0.27 mg group, 1 subject in the 0.675 mg/kg group, 0 subjects in the 1.35 mg/kg group, 1 subject in the 2.7 mg/kg group, 1 subject in the placebo group).

4.(ii).A.(2).3) Phase II study (5.3.5.1.1, C0379T04 [June 2003 to March 2005])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 300 [60 subjects per group]) to evaluate the efficacy and safety of ustekinumab.

According to Table 16, 45 or 90 mg[18] of ustekinumab or placebo was to be administered subcutaneously. Subjects were followed for safety and efficacy through Week 32 and Week 36, respectively.

In Study T01, 2 of 4 subjects in the 0.27 mg/kg group achieved a PASI 75 response and the bioavailability of ustekinumab following subcutaneous administration was approximately 62.5% and the mean body weight of psoriasis patients was approximately 95 kg. Taking account of these findings, an ustekinumab subcutaneous fixed dose of 45 mg was selected as the lowest dose for this study. Since subjects with AUC_{∞} >450 μg·day/mL or C_{max} >27 μg/mL achieved a PASI 75 response in Studies T01 and T02, a compartment model analysis was performed using the data from the two studies and 90 mg (single dose), 180 mg (45 mg/week × 4), and 360 mg (90 mg/week × 4) as well as 45 mg (single dose) were selected to span the above-mentioned levels of AUC_{∞} and C_{max}.

Table 16. Ustekinumab dosing schedule for each treatment group

	Week 0	Weeks 1, 2, 3	Week 16	Week 20
45 mg single-dose group	Ustekinumab 45 mg	Placebo	Ustekinumab 45 mg or placebo[a]	Placebo
90 mg single-dose group	Ustekinumab 90 mg	Placebo	Ustekinumab 90 mg or placebo[a]	Placebo
45 mg multiple-dose group	Ustekinumab 45 mg	Ustekinumab 45 mg	Ustekinumab 45 mg or placebo[a]	Placebo
90 mg multiple-dose group	Ustekinumab 90 mg	Ustekinumab 90 mg	Ustekinumab 90 mg or placebo[a]	Placebo
Placebo group	Placebo	Placebo	Placebo	Ustekinumab 90 mg

a: Subjects with relative PGA ≥3 were to receive ustekinumab and subjects with relative PGA <3 were to receive placebo.

[18] Although the study was intended to be conducted at doses of 50 and 100 mg of ustekinumab, the absorption coefficient used to measure antibody concentration was corrected from 1.40 $(mg/mL)^{-1}cm^{-1}$ to 1.54 $(mg/mL)^{-1}cm^{-1}$ after the completion of the clinical study, which leaded to correction of the previously determined concentration of the formulation of ustekinumab.

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The efficacy population included 320 randomized subjects (64 subjects per group). Excluding 2 subjects who did not receive study drug (1 subject each in the 45 mg single-dose and 90 mg single-dose groups) and including 1 subject who mistakenly received placebo before randomization, 319 subjects were included in the safety population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 was 51.6% (33 of 64 subjects) in the 45 mg single-dose group, 59.4% (38 of 64 subjects) in the 90 mg single-dose group, 67.2% (43 of 64 subjects) in the 45 mg multiple-dose group, 81.3% (52 of 64 subjects) in the 90 mg multiple-dose group, and 1.6% (1 of 64 subjects) in the placebo group and subjects treated with ustekinumab showed significantly greater improvement compared with subjects treated with placebo ($P < 0.001$, pairwise comparisons using the Chochran-Mantel-Haenzel χ^2 test).

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 36 were 95.2% (60 of 63 subjects) in the 45 mg single-dose group, 87.5% (56 of 64 subjects) in the 90 mg single-dose group, 87.3% (55 of 63 subjects) in the 45 mg multiple-dose group, 72.6% (45 of 62 subjects) in the 90 mg multiple-dose group, 51.0% (25 of 49 subjects) in the placebo→90 mg (after Week 20) group, and 71.6% (48 of 67 subjects) in the placebo group (through Week 20). No deaths were reported. The incidences of serious adverse events were 4.8% (3 of 63 subjects) (acute psychosis; cellulitis; and rib fracture, 1 subject each) in the 45 mg single-dose group, 4.7% (3 of 64 subjects) (myocardial infarction; abdominal hernia; and coronary artery disease, 1 subject each) in the 90 mg single-dose group, 3.2% (2 of 63 subjects) (cerebrovascular accident; and chest pain, 1 subject each) in the 45 mg multiple-dose group, 8.1% (5 of 62 subjects) (urinary tract infection; acute myocardial infarction and viral infection; uterine leiomyoma; pneumonia and cardiac failure congestive; and acute psychosis and polysubstance dependence, 1 subject each) in the 90 mg multiple-dose group, 2.0% (1 of 49 subjects) (hepatic enzyme increased) in the placebo→90 mg (after Week 20) group, and 1.5% (1 of 67 subjects) (psoriasis) in the placebo group and a causal relationship to study drug could not be denied for cellulitis, myocardial infarction, coronary artery disease, cerebrovascular accident, urinary tract infection, acute myocardial infarction, viral infection, pneumonia, cardiac failure congestive, and hepatic enzyme increased. The outcomes of coronary artery disease, cardiac failure congestive, acute psychosis, and polysubstance dependence were reported as unresolved, but other events resolved. The incidences of adverse events leading to treatment discontinuation were 14.3% (9 of 63 subjects) in the 45 mg single-dose group, 1.6% (1 of 64 subjects) in the 90 mg single-dose group, 1.6% (1 of 63 subjects) in the 45 mg multiple-dose group, 1.6% (1 of 62 subjects) in the 90 mg multiple-dose group, and 3.0% (2 of 67 subjects) in the placebo group, and those reported by ≥2 subjects were psoriasis (2 subjects in the 45 mg single-dose group, 2 subjects in the placebo group).

The incidences of adverse drug reactions were 74.6% (47 of 63 subjects) in the 45 mg single-dose group, 68.8% (44 of 64 subjects) in the 90 mg single-dose group, 63.5% (40 of 63 subjects) in the 45 mg multiple-dose group, 48.4% (30 of 62 subjects) in the 90 mg multiple-dose group, 24.5% (12 of 49

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subjects) in the placebo→90 mg (after Week 20) group, and 46.3% (31 of 67 subjects) in the placebo group (through Week 20), and those reported by ≥5% of subjects in any group were as shown in Table 17.

Table 17. Adverse drug reactions reported by ≥5% of subjects in any group

Preferred terms	Placebo (Weeks 0-20)	Placebo→90mg (after Week 20)	45 mg single dose	90 mg single dose	45 mg multiple doses	90 mg multiple doses
Nasopharyngitis	5 (7.5)	0	5 (7.9)	7 (10.9)	3 (4.8)	5 (8.1)
Upper respiratory tract infection	4 (6.0)	0	7 (11.1)	5 (7.8)	6 (9.5)	3 (4.8)
Urinary tract infection	0	0	3 (4.8)	1 (1.6)	4 (6.3)	3 (4.8)
Arthralgia	0	2 (4.1)	5 (7.9)	3 (4.7)	0	3 (4.8)
Myalgia	0	0	4 (6.3)	1 (1.6)	0	1 (1.6)
Arthritis	4 (6.0)	0	1 (1.6)	1 (1.6)	0	0
Pruritus	1 (1.5)	0	7 (11.1)	3 (4.7)	1 (1.6)	2 (3.2)
Headache	8 (11.9)	0	12 (19.0)	9 (14.1)	0	10 (16.1)
Diarrhoea	0	0	2 (3.2)	0	4 (6.3)	1 (1.6)
Nausea	2 (3.0)	0	1 (1.6)	3 (4.7)	2 (3.2)	4 (6.5)

n (%)

4.(ii).A.(2).4) Phase II clinical study (5.3.5.4.1, C0743T10 [December 2005 to September 2007])

A placebo-controlled, randomized, double-blind study was conducted in patients with active psoriatic arthritis (Target sample size of 140 [70 subjects per group]) to evaluate the efficacy and safety of ustekinumab.

In Group I (ustekinumab→placebo group), 90 mg[19] of ustekinumab at Weeks 0, 1, 2, and 3 and placebo at Weeks 12 and 16 were to be administered subcutaneously. In Group II (placebo→ustekinumab group), placebo at Weeks 0, 1, 2, and 3 and 90 mg[19] of ustekinumab at Weeks 12 and 16 were to be administered subcutaneously. Subjects were followed for efficacy and safety through Week 36.

All of the 146 subjects treated (76 subjects in the ustekinumab→placebo group, 70 subjects in the placebo→ustekinumab group) were included both in the safety and primary efficacy populations.

The primary efficacy endpoint of the ACR 20 response rate at Week 12 was 42.1% (32 of 76 subjects) in the ustekinumab group, which was significantly higher than 14.3% (10 of 70 subjects) in the placebo group ($P < 0.001$).

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 60.5% (46 of 76 subjects) (107 events) in the ustekinumab group and 62.9% (44 of 70 subjects) (89 events) in the placebo group. No deaths were reported. The incidences of serious adverse events were 0% (0 of 76 subjects) (0 events) in the ustekinumab group and 4.3% (3 of 70 subjects) (3

[19] During this clinical study, it was revealed that the vials of another study drug that was not used in this study contained particulate matters. Since the lyophilized formulation of ustekinumab was also filled at the same site over the same period of time, as a precautionary measure to ensure subject's safety, the prepared solution for injection was filtered. The volume of the filtered solution for injection was approximately 0.70 mL (corresponding to 63 mg of ustekinumab). In Group I, 59 of 76 subjects received the filtered solution (63 mg of ustekinumab) for all 4 doses and 3 of the remaining 17 subjects received the filtered solution (63 mg of ustekinumab) for at least one of the 4 doses. Of 70 subjects in Group II, 57 subjects at Week 12 and 55 subjects at Week 16 received the filtered solution (63 mg of ustekinumab).

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events) (myocardial infarction, gastric ulcer haemorrhage, chest pain) in the placebo group and although a causal relationship to study drug could not be denied for all events, the outcomes of all events were reported as resolved. The incidences of adverse events leading to treatment discontinuation were 1.3% (1 of 76 subjects) (1 event) (pregnancy) in the ustekinumab group and 5.7% (4 of 70 subjects) (4 events) (psoriatic arthropathy [2 events], chest pain [1 event], psoriasis [1 event]) in the placebo group, and a causal relationship to study drug could not be denied for 1 event of chest pain and 1 event of psoriatic arthropathy in the placebo group and the outcome of 1 event of psoriasis in the placebo group was reported as unresolved, but other events all resolved.

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 36 were 76.3% (58 of 76 subjects) (204 events) in the ustekinumab→placebo group and 63.2% (36 of 57 subjects) (90 events) in the placebo→ustekinumab group[20]. No deaths were reported. The incidences of serious adverse events from Week 12 through Week 36 were 7.9% (6 of 76 subjects) (10 events) in the ustekinumab group (including subjects crossed over from placebo to ustekinumab) and 1.8% (1 of 57 subjects) (1 event) (pelvic mass) in the placebo→ustekinumab group (a subject who did not receive ustekinumab), and a causal relationship to study drug could not be denied for all events, but the outcomes of all events except for haemorrhagic stroke (1 subject) were reported as resolved. The incidence of adverse events leading to treatment discontinuation was 3.9% (3 of 76 subjects) (3 events) (abdominal pain; basal cell carcinoma; and haemorrhagic stroke, 1 subject each) in the ustekinumab group and a causal relationship to study drug could not be denied for all events and the outcomes of all events except for haemorrhagic stroke (1 subject) were reported as resolved.

The incidences of adverse drug reactions through Week 36 were 55.3% (42 of 76 subjects) (111 events) in the ustekinumab→placebo group and 45.6% (26 of 57 subjects) (61 events) in the placebo→ustekinumab group and those reported by ≥5% of subjects in any group were as shown in Table 18.

Table 18. Adverse drug reactions reported by ≥5% of subjects in any group

Preferred terms	Placebo (Weeks 0-12)	Placebo→Ustekinumab (Weeks 12-36)	Ustekinumab (Weeks 0-36)
Upper respiratory tract infection	4 (5.7)	5 (8.8)	7 (9.2)
Nasopharyngitis	3 (4.3)	3 (5.3)	6 (7.9)
Influenza	4 (5.7)	1 (1.8)	1 (1.3)
Diarrhoea	1 (1.4)	1 (1.8)	4 (5.3)
Nausea	0	3 (5.3)	2 (2.6)
Alanine aminotransferase increased	1 (1.4)	1 (1.8)	4 (5.3)
Headache	3 (4.3)	1 (1.8)	4 (5.3)

n (%)

4.(ii).A.(2).5) Phase III clinical study (5.3.5.1.3, C0743T08 [December 2005 to ongoing (data cut-off of March 2009)])

A placebo-controlled, randomized, double-blind study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 750 [250 subjects per group]) to evaluate the efficacy

[20] From Week 12 through Week 36, after crossover to ustekinumab.

and safety of ustekinumab and the interim report (through Week 152) (March 2009) of the study was submitted.

Forty-five or 90 mg of ustekinumab or placebo was to be administered subcutaneously according to Figure 2. A long-term extension period began at Week 52 and subjects were to continue to receive the same dose and schedule of ustekinumab that they were receiving at Week 52. Subjects randomized to placebo at Week 40 were to begin retreatment with ustekinumab every 12 weeks at loss of therapeutic effect as assessed by the PASI score.

In Study T04, the PASI 75 response rates at Week 12 in the 45 mg (single dose), 90 mg (single dose), 180 mg (45 mg/week × 4), and 360 mg (90 mg/week × 4) groups were 51.6%, 59.4%, 67.2%, and 81.3%, respectively, and a dose response relationship was observed with approximately 10% increments in PASI 75 response rate observed with every doubling in exposure between 45 mg and 360 mg. Thus, for foreign phase III studies (Studies T08 and T09), "45 or 90 mg of ustekinumab subcutaneously administered at Weeks 0 and 4" corresponding to the medium exposures tested in Study T04 (90 mg and 180 mg) was selected as the initial dosing regimen. Since efficacy peaked at around Week 12 in Study T04, the initial dosing regimen followed by the same dose every 12 weeks was proposed.

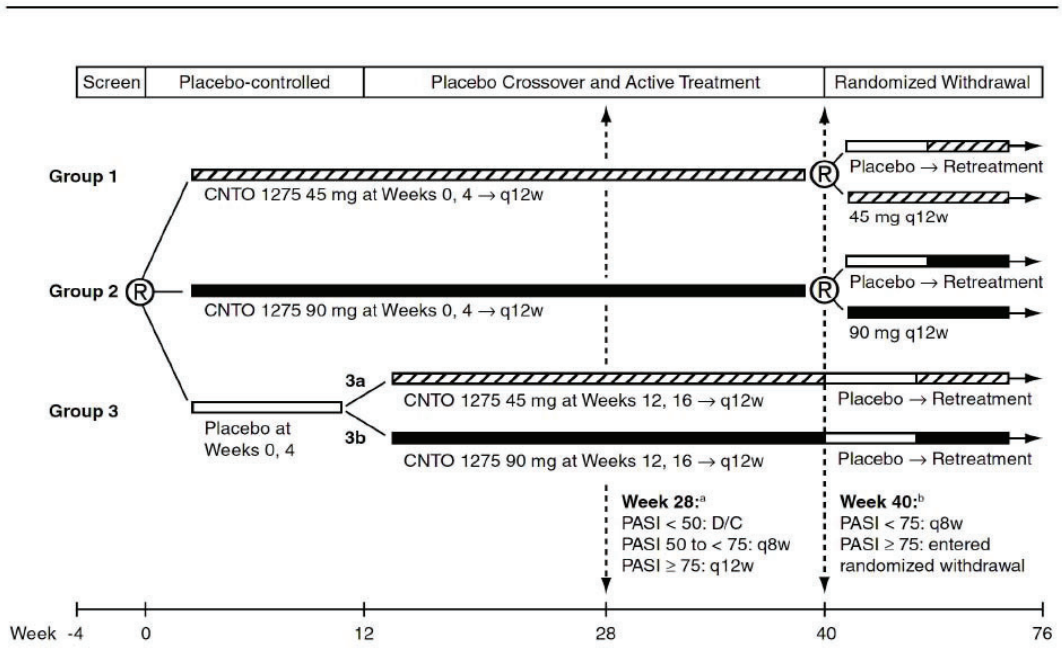


Figure 2. Study design and dosing schedule for Foreign Study T08
Group 1: 45 mg group, Group 2: 90 mg group, Group 3: placebo group, D/C: discontinuation, Ⓡ: randomization, q8w: every 8 weeks, q12w: every 12 weeks, CNTO 1275: ustekinumab
a: At Week 28, in all Groups, nonresponders discontinued study drug, partial responders began q8w dosing, and responders continued q12w dosing.
b: At Week 40, responders to q12w dosing in Groups 1 and 2 were randomized to either placebo or continued q12w ustekinumab (at their original dose) and subjects in Group 3 received placebo. At loss of therapeutic effect, subjects receiving placebo began retreatment (at their dosing regimen prior to Week 40). In all Groups, nonresponders or partial responders began q8w dosing. Subjects receiving q8w dosing continued q8w dosing.

The primary efficacy population included 766 randomized subjects (45 mg group [Group 1 as in Figure 2] 255 subjects; 90 mg group [Group 2 as in Figure 2] 256 subjects; placebo group [Group 3a or 3b as in Figure 2] 255 subjects) while 765 subjects, excluding 1 subject who did not receive study drug (90 mg group), were included in the safety population.

The primary efficacy endpoint of the PASI 75 response rate at Week 12 (%) was as shown in Table 19 and the response rate was significantly higher in the ustekinumab groups compared to the placebo group ($P < 0.001$, pairwise comparisons using the Cochran-Mantel-Haenszel χ^2 test). The secondary endpoints of the PASI 50 response rate and the PASI 90 response rate were as shown in Table 19.

Table 19. PASI response rate at Week 12

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
PASI 50 response rate	10.2 (26/255)	83.5 (213/255)	85.9 (220/256)
PASI 75 response rate	3.1 (8/255)	67.1 (171/255)	66.4 (170/256)
PASI 90 response rate	2.0 (5/255)	41.6 (106/255)	36.7 (94/256)

% (n)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 57.6% (147 of 255 subjects) (302 events) in the 45 mg group, 51.4% (131 of 255 subjects) (269 events) in the 90 mg group, and 48.2% (123 of 255 subjects) (224 events) in the placebo group. No deaths were reported. Serious adverse events were reported by 2 subjects in the 45 mg group (cerebrovascular accident; and hypertension, 1 subject each), 4 subjects in the 90 mg group (herpes zoster disseminated; cellulitis; coronary artery disease; and psoriasis, 1 subject each), and 2 subjects in the placebo group (psychotic disorder; and pneumonia, 1 subject each), and a causal relationship to study drug could not be denied for any of these events except for coronary artery disease, but the outcomes of all events were reported as resolved. The incidences of adverse events leading to treatment discontinuation were 0.4% (1 of 255 subjects) (cerebrovascular accident) in the 45 mg group, 1.6% (4 of 255 subjects) (herpes zoster disseminated; cellulitis; pregnancy; and dyspepsia, 1 subject each) in the 90 mg group, and 2.4% (6 of 255 subjects) (psoriasis [2 subjects], dermatitis exfoliative [2 subjects], psychotic disorder [1 subject], rash generalised [1 subject]) in the placebo group, and a causal relationship to study drug could not be denied for any of these events except for pregnancy, but the outcomes of all events except for pregnancy were reported as resolved.

The incidences of adverse drug reactions were 35.3% (90 of 255 subjects) (163 events) in the 45 mg group, 30.6% (78 of 255 subjects) (162 events) in the 90mg group, and 27.1% (69 of 255 subjects) (125 events) in the placebo group and those reported by ≥2% of subjects in any group were as shown in Table 20.

Table 20. Adverse drug reactions reported by ≥2% of subjects in any group (through Week 12)

Preferred terms	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
Upper respiratory tract infection	9 (3.5)	11 (4.3)	12 (4.7)
Nasopharyngitis	8(3.1)	9 (3.5)	9 (3.5)
Headache	5(2.0)	12 (4.7)	11 (4.3)
Dizziness	1 (0.4)	5 (2.0)	3 (1.2)
Fatigue	3 (1.2)	4 (1.6)	6 (2.4)
Injection site erythema	2 (0.8)	0	7 (2.7)
Arthralgia	6 (2.4)	4 (1.6)	6 (2.4)

n (%)

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The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 152 were 92.1% (348 of 378 subjects) (2481 events) in the 45 mg group[21] and 90.9% (341 of 375 subjects) (2400 events) in the 90 mg group[22]. Two subjects in the placebo→90 mg group (respiratory failure, pneumonia, chronic hepatic failure, and colitis; and completed suicide) and 1 subject in the 90 mg group (intestinal perforation) died, but a causal relationship to study drug was denied for all cases. The incidences of serious adverse events were 7.9% (30 of 378 subjects) in the 45 mg group and 10.1% (38 of 375 subjects) in the 90 mg group, and those reported by ≥2 subjects in either group were coronary artery disease (7 subjects in the 90 mg group), prostate cancer (3 subjects in the 45 mg group), cellulitis (2 subjects in the 90 mg group), osteomyelitis (2 subjects in the 90 mg group), myocardial infarction (2 subjects in the 90 mg group), and cerebrovascular accident (2 subjects in the 45 mg group). The incidences of adverse events leading to treatment discontinuation from Week 0 through Week 152 were 6.9% (26 of 378 subjects) in the 45 mg group and 6.4% (24 of 375 subjects) in the 90 mg group.

The incidences of adverse drug reactions were 62.4% (236 of 378 subjects) (1116 events) in the 45 mg group and 62.9% (236 of 375 subjects) (1073 events) in the 90 mg group and those reported by ≥2% of subjects in either group were as shown in Table 21.

Table 21. Adverse drug reactions reported by ≥2% of subjects in either group (through Week 152)

Preferred terms	Ustekinumab 45 mg	Ustekinumab 90 mg
Nasopharyngitis	35 (9.3)	45 (12.0)
Upper respiratory tract infection	69 (18.3)	64 (17.1)
Sinusitis	21 (5.6)	18 (4.8)
Influenza	17 (4.5)	16 (4.3)
Gastroenteritis	19 (5.0)	14 (3.7)
Bronchitis	16 (4.2)	15 (4.0)
Pharyngitis	9 (2.4)	9 (2.4)
Urinary tract infection	10 (2.6)	7 (1.9)
Arthralgia	27 (7.1)	19 (5.1)
Psoriatic arthropathy	9 (2.4)	4 (1.1)
Arthritis	9 (2.4)	6 (1.6)
Back pain	9 (2.4)	12 (3.2)
Pain in extremity	6 (1.6)	8 (2.1)
Diarrhoea	8 (2.1)	14 (3.7)
Oropharyngeal pain	6 (1.6)	9 (2.4)
Nasal congestion	5 (1.3)	8 (2.1)
Headache	29 (7.7)	22 (5.9)
Dizziness	11 (2.9)	11 (2.9)
Injection site erythema	14 (3.7)	19 (5.1)
Fatigue	15 (4.0)	10 (2.7)
Night sweats	9 (2.4)	7 (1.9)
Cough	12 (3.2)	11 (2.9)
Alanine aminotransferase increased	7 (1.9)	8 (2.1)
Insomnia	8 (2.1)	8 (2.1)
Hypertension	17 (4.5)	16 (4.3)

n (%)

[21] A group of subjects who received 45 mg of ustekinumab by Week 152 (Group 1 and Group 3a). After Week 12 (after crossover to ustekinumab) for Group 3a.

[22] A group of subjects who received 90 mg of ustekinumab by Week 152 (Group 2 and Group 3b). After Week 12 (after crossover to ustekinumab) for Group 3b.

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4.(ii).A.(2).6) Phase III study (5.3.5.1.4, C0743T09 [March 2006 to ongoing (data cut-off of August 2008)])

A placebo-controlled, randomized, double-blind study was conducted in patients with moderate to severe plaque psoriasis (Target sample size of 1200 [400 subjects per group]) to evaluate the efficacy and safety of ustekinumab and the interim report (through Week 100) (August 2008) of the study was submitted.

Forty-five or 90 mg of ustekinumab or placebo was to be administered subcutaneously according to Figure 3. A long-term extension period began at Week 52 and after the unblinding, adjustment of each subject's dosing regimen was allowed at the investigator's discretion. The duration of treatment was up to 264 weeks.

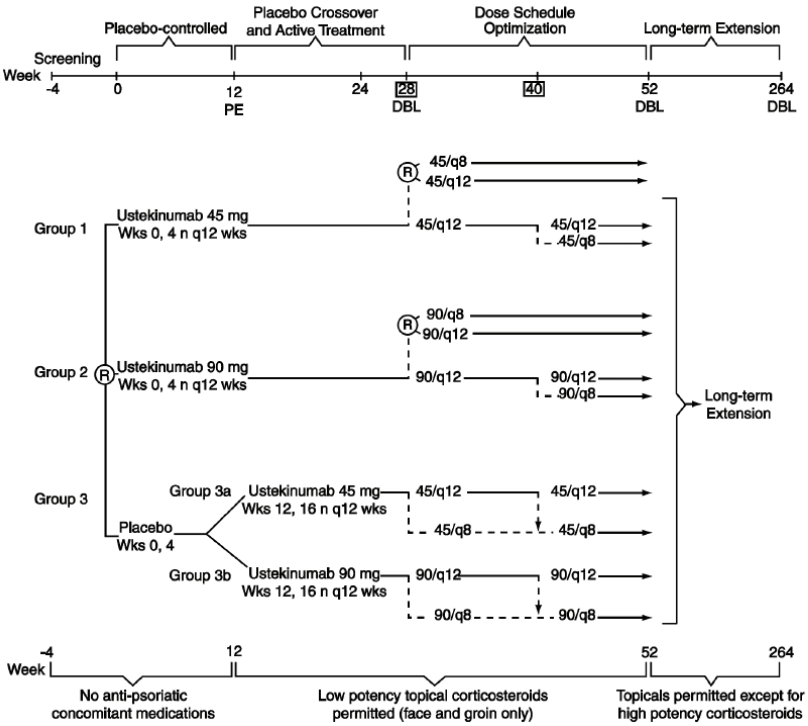


Figure 3. Study design and dosing schedule for Foreign Study T09
Group 1: 45 mg group, Group 2: 90 mg group, Group 3: placebo group, Ⓡ: randomization, PE: primary endpoint, DBL: database lock, q8: every 8 weeks, q12: every 12 weeks.
At Week 28, in all Groups, nonresponders discontinued study treatment. In Groups 1 and 2, partial responders were randomized to either q8wk or q12wk dosing. In Group 3, partial responders began q8wk dosing.
At Week 40, among responders at Week 28 in all Groups, nonresponders and partial responders began q8wk dosing.

The safety population and the primary efficacy population included 1230 randomized subjects (45 mg group [Group 1 as in Figure 3] 409 subjects; 90 mg group [Group 2 as in Figure 3] 411 subjects; placebo group [Group 3a or 3b as in Figure 3] 205 subjects each).

The primary efficacy endpoint of the PASI 75 response rate (%) at Week 12 was as shown in Table 22 and the response rate was significantly higher in the ustekinumab groups compared to the placebo

group ($P < 0.001$, pairwise comparisons using the Cochran-Mantel-Haenszel χ^2 test). The secondary endpoints of the PASI 50 resposne rate and the PASI 90 response rate were as shown in Table 22.

Table 22. PASI response rates at Week 12

	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
PASI 50 response rate	10.0 (41/410)	83.6 (342/409)	89.3 (367/411)
PASI 75 response rate	3.7 (15/410)	66.7 (273/409)	75.7 (311/411)
PASI 90 response rate	0.7 (3/410)	42.3 (173/409)	50.9 (209/411)

% (n)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 12 were 53.1% (217 of 409 subjects) (402 events) in the 45 mg group, 48.7% (200 of 411 subjects) (408 events) in the 90 mg group, and 49.8% (204 of 410 subjects) (365 events) in the placebo group. The incidences of serious adverse events were 2.0% (8 of 409 subjects) (intervertebral disc protrusion [2 subjects], angina pectoris; nephrolithiasis; seroma; dactylitis; sciatica; and clavicle fracture, 1 subject each) in the 45 mg group, 1.2% (5 of 411 subjects) (congestive cardiomyopathy; meningioma benign; cellulitis; alcohol withdrawal syndrome; and hypertension, palpitations, ventricular extrasystoles, and vertigo, 1 subject each) in the 90 mg group, and 2.0% (8 of 410 subjects) (cellulitis [2 subjects], hepatic neoplasm malignant and ascites; asthma; cervicobrachial syndrome; chest pain; psoriatic arthropathy; and pityriasis rubra pilaris, 1 subject each) in the placebo group and a causal relationship to study drug could not be denied for any of these events except for intervertebral disc protrusion (2 subjects), angina pectoris, nephrolithiasis, and seroma in the 45 mg group, meningioma benign and alcohol withdrawal syndrome in the 90 mg group, and hepatic neoplasm malignant and ascites; cervicobrachial syndrome; chest pain; and pityriasis rubra pilaris in the placebo group and the outcomes of all events were reported as resolved except for congestive cardiomyopathy (death) in the 90 mg group and hepatic neoplasm malignant and ascites; and psoriatic arthropathy (all unresolved) in the placebo group. The incidences of adverse events leading to treatment discontinuation were 0.2% (1 of 409 subjects) (1 event) (neutropenia) in the 45 mg group, 1.5% (6 of 411 subjects) (10 events) (pneumonia; basal cell carcinoma; hepatitis; meningioma benign; hypertension, palpitations, ventricular extrasystoles, and vertigo; and alcohol abuse and alcohol withdrawal syndrome, 1 subject each) in the 90 mg group, and 1.7% (7 of 410 subjects) (7 events) (psoriasis [2 subjects], pustular psoriasis; cellulitis; pregnancy; ascites; and psoriatic arthropathy, 1 subject each) in the placebo group, and a causal relationship to study drug could not be denied for all events except for pregnancy and ascites in the placebo group and basal cell carcinoma; meningioma benign; and alcohol abuse and alcohol withdrawal syndrome in the 90 mg group and the outcomes of all events except for ascites, pustular psoriasis, and psoriatic arthropathy in the placebo group were reported as resolved.

The incidences of adverse drug reactions (including abnormal laboratory test values) were 34.5% (141 of 409 subjects) in the 45 mg group, 32.8% (135 of 411 subjects) in the 90 mg group, and 29.5% (121 of 410 subjects) in the placebo group and those reported by ≥2% of subjects in any group were as shown in Table 23.

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Table 23. Adverse drug reactions reported by ≥2% of subjects in any group (through Week 12)

Preferred terms	Placebo	Ustekinumab 45 mg	Ustekinumab 90 mg
Nasopharyngitis	18 (4.4)	15 (3.7)	13 (3.2)
Upper respiratory tract infection	8 (2.0)	10 (2.4)	7 (1.7)
Diarrhoea	8 (2.0)	7 (1.7)	10 (2.4)
Headache	12 (2.9)	19 (4.6)	13 (3.2)
Fatigue	8 (2.0)	11 (2.7)	10 (2.4)
Arthralgia	5 (1.2)	12 (2.9)	8 (1.9)

n (%)

The incidences of adverse events (including abnormal laboratory test values) from Week 0 through Week 100 were 90.4% (548 of 606 subjects) (2883 events) in the 45 mg group[23] and 90.4% (548 of 606 subjects) (2956 events) in the 90 mg[24] group. One subject in the placebo→45 mg group (aspiration), 1 subject in the placebo→90 mg group (metastatic renal cancer), and 2 subjects in the 90 mg group (shock, congestive cardiomyopathy) died and a causal relationship to study drug was denied for all events except for congestive cardiomyopathy. The incidences of serious adverse events were 10.1% (61 of 606 subjects) in the 45 mg group and 9.2% (56 of 606 subjects) in the 90 mg group and those reported by ≥2 subjects in either group were as shown in Table 24. The incidences of serious adverse events for which a causal relationship to study drug could not be denied were 2.5% (15 of 606 subjects) in the 45 mg group and 2.6% (16 of 606 subjects) in the 90 mg group. The incidences of adverse events leading to treatment discontinuation were 3.3% (20 of 606 subjects) in the 45 mg group and 5.4% (33 of 606 subjects) in the 90 mg group.

The incidences of adverse drug reactions (including abnormal laboratory test values) were 62.9% (381 of 606 subjects) in the 45 mg group and 63.7% (386 of 606 subjects) in the 90 mg group, and those reported by ≥2% of subjects in either group were as shown in Table 25.

Table 24. Serious adverse events reported by ≥2 subjects in either group (through Week 100)

Preferred terms	Ustekinumab 45 mg	Ustekinumab 90 mg
Coronary artery disease	4 (0.7)	1 (0.2)
Angina unstable	2 (0.3)	2 (0.3)
Myocardial infarction	2 (0.3)	1 (0.2)
Prostate cancer	1 (0.2)	2 (0.3)
Cellulitis	2 (0.3)	1 (0.2)
Diverticulitis	1 (0.2)	2 (0.3)
Abdominal pain	2 (0.3)	0
Chest pain	2 (0.3)	6 (1.0)
Nephrolithiasis	3 (0.5)	1 (0.2)
Renal colic	1 (0.2)	2 (0.3)
Intervertebral disc protrusion	4 (0.7)	0

n (%)

Table 25. Adverse drug reactions reported by ≥2% of subjects in either group (through Week 100)

Preferred terms	Ustekinumab 45 mg	Ustekinumab 90 mg
Nasopharyngitis	93 (15.3)	101 (16.7)
Upper respiratory tract infection	96 (15.8)	90 (14.9)
Influenza	34 (5.6)	38 (6.3)
Bronchitis	28 (4.6)	23 (3.8)
Sinusitis	20 (3.3)	27 (4.5)
Gastroenteritis	23 (3.8)	21 (3.5)
Pharyngitis	7 (1.2)	12 (2.0)
Urinary tract infection	9 (1.5)	13 (2.1)
Oral herpes	13 (2.1)	7 (1.2)

[23] A group of subjects who received 45 mg of ustekinumab by Week 100 (Group 1 and Group 3a).

[24] A group of subjects who received 90 mg of ustekinumab by Week 100 (Group 2 and Group 3b).

Back pain	19 (3.1)	25 (4.1)
Arthralgia	33 (5.4)	36 (5.9)
Myalgia	11 (1.8)	14 (2.3)
Pain in extremity	13 (2.1)	10 (1.7)
Skeletal muscle pain	12 (2.0)	6 (1.0)
Chest pain	4 (0.7)	17 (2.8)
Diarrhoea	25 (4.1)	23 (3.8)
Pruritus	11 (1.8)	16 (2.6)
Night sweats	5 (0.8)	14 (2.3)
Fatigue	24 (4.0)	20 (3.3)
Injection site erythema	22 (3.6)	25 (4.1)
Headache	46 (7.6)	38 (6.3)
Dizziness	10 (1.7)	16 (2.6)
Cough	22 (3.6)	27 (4.5)
Pharyngolaryngeal pain	14 (2.3)	20 (3.3)
Hypertension	25 (4.1)	29 (4.8)

n (%)

4.(ii).B Outline of the review

4.(ii).B.(1) Efficacy

4.(ii).B.(1).1) Efficacy in the treatment of psoriasis vulgaris and plaque psoriasis in psoriatic arthritis

PMDA concludes that based on the submitted study data, the efficacy of ustekinumab in the treatment of psoriasis vulgaris and plaque psoriasis in psoriatic arthritis has been demonstrated.

4.(ii).B.(1).2) Efficacy of ustekinumab in reducing joint symptoms of psoriatic arthritis

While the treatment of joint symptoms as well as skin symptoms is considered important in psoriatic arthritis, pain VAS assessment only was performed in Japanese Study JPN-02 and the efficacy of ustekinumab in reducing joint symptoms has not been confirmed overseas either. PMDA asked the applicant to explain their view on the expected degree of efficacy of ustekinumab in reducing joint symptoms.

The applicant explained as follows:

In Japanese Study JPN-02, 22 subjects who were confirmed by the investigator or sub-investigator to have joint symptoms at Week 0 (3 subjects in the placebo group, 6 subjects in the 45 mg group, 13 subjects in the 90 mg group) were assessed for pain VAS score. As a result, the median changes from baseline at Week 12 (mean ± SD) were 1.0 (8.0 ± 13.00) in the placebo group, -41.0 (-38.5 ± 28.93) in the 45 mg group, and -10.0 (-9.3 ± 18.23) in the 90 mg group, and ustekinumab tended to reduce joint pain, though the number of subjects assessed was small. In a foreign phase II clinical study that evaluated the efficacy of ustekinumab in reducing the symptoms and signs of arthritis in patients with active psoriatic arthritis (Study T10), the primary endpoint of the ACR 20 response rate at Week 12 was significantly higher in the ustekinumab group (42.1% [32 of 76 subjects]) compared to the placebo group (14.3% [10 of 70 subjects]) ($P < 0.001$, Cochran-Mantel-Haenszel $\chi 2$ test), suggesting the efficacy of ustekinumab in reducing joint symptoms. These results are not substantially different from the results from adalimumab or infliximab foreign phase II and III studies in patients with active psoriatic arthritis (Table 26).

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Table 26. Comparison of efficacy of ustekinumab vs. other biologics
based on foreign placebo-controlled, double-blind studies in patients with psoriatic arthritis

Summary of study											
Product	Ustekinumab			Infliximab				Adalimumab			
Study ID	Foreign phase II clinical study (C0743T10)			Phase II clinical study (IMPACT)		Phase III clinical study (IMPACT2)		Phase III clinical study (Study M02-518)		Phase III clinical study (Study M02-570)	
Main dosing regimen	ustekinumab 90 mg (63 mg)* or placebo subcutaneously administered at Weeks 0, 1, 2, and 3 and then crossover to placebo or ustekinumab 90 mg (63 mg) subcutaneously administered at Weeks 12 and 16			infliximab 5 mg/kg or placebo given as an intravenous infusion at Weeks 0, 2, 6, and 14		infliximab 5 mg/kg or placebo given as an intravenous infusion at Weeks 0, 2, 6, 14, and 22		adalimumab 40 mg or placebo subcutaneously administered every other week		adalimumab 40 mg or placebo subcutaneously administered every other week	
Primary endpoint	ACR 20 response rate (Week 12)			ACR 20 response rate (Week 16)		ACR 20 response rate (Week 14)		ACR 20 response rate (Week 12)		ACR 20 response rate (Week 12)	
Study results											
Treatment group	Placebo	Ustekinumab 90 mg (63 mg)	Placebo →90 mg (63 mg)[a]	Placebo	infliximab 5 mg/kg	Placebo	infliximab 5 mg/kg	Placebo	adalimumab 40 mg	Placebo	adalimumab 40 mg
Number of subjects	70	76	55	52	52	100	100	162	151	49	51
ACR 20 response rate	14.3%	42.1%	50.9%	9.6%	65.4%	11.0%	58.0%	14%	58%	16%	39%
Pain VAS score (SD)	-13.17 (62.141) [b]	21.38 (65.579) [b]	29.23 (49.817) [b]	-8.7 (7.8) [b]	53.7 (7.7) [b]	-11.8 (109.8) [b]	39.6 (56.1) [b]	—	—	0.2 (23.1) [c]	-15.4 (25.6) [c]

a: Assessment at Week 24 (12 weeks after crossover to ustekinumab) for subjects crossed over from placebo to ustekinumab at Week 12,
b: mean percent improvement (SD), c: mean change (SD)
* During this clinical study, it was revealed that the vials of another study drug that was not used in this study contained particulate matters. Since the lyophilized formulation of ustekinumab used in this study was also filled at the same site over the same period of time, as a precautionary measure to ensure subject's safety, the prepared solution for injection was filtered (pore size, 0.22 μm). The volume of the filtered solution for injection was approximately 0.70 mL (corresponding to 63 mg of ustekinumab).

Furthermore, in Study T10 and foreign studies of adalimumab and infliximab, changes in pain VAS score were measured as an ACR core set variable. As a result, as shown in Table 26, improvement in joint pain as measured by pain VAS score as well as improvement in joint symptoms as measured by the primary endpoint of the ACR 20 response rate was observed simultaneously in all studies. Based on the above, though pain VAS assessment only was performed in Japanese Study JPN-02, the efficacy of ustekinumab in reducing joint symptoms can be expected also in Japanese patients with psoriatic arthritis.

The applicant also responded as follows:
Two foreign phase III studies to confirm the efficacy of ustekinumab (45 mg and 90 mg) in improving the symptoms and signs of arthritis and preventing joint structural damage progression in patients with active psoriatic arthritis are currently ongoing.

In Japanese Study JPN-02, subjects with joint symptoms at Week 0, regardless of a diagnosis of psoriatic arthritis, were assessed for pain VAS score. PMDA asked the applicant to also explain the results from subjects diagnosed with psoriatic arthritis.

The applicant explained as follows:

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Usually, patients who develop psoriatic arthritis have skin symptoms of psoriasis first, followed by joint symptoms several years later and the statistics of psoriasis patients in Japan report that only 1.0% of the patients are diagnosed with psoriatic arthritis at the first visit (Hashimoto Y. *Dermatology Practice 16 Psoriasis*. 2004;215-9). Based on patients registered with the Japanese Society for Psoriasis Research from 1999 to 2002 (4 years), 2.0% of the patients were diagnosed with psoriatic arthritis at the first visit while 7.6% of the patients had joint symptoms. Taking account of these findings, subjects who were confirmed by the investigator or sub-investigator to have joint symptoms, regardless of a diagnosis of psoriatic arthritis, were assessed for pain VAS score in Japanese Study JPN-02. Of 14 subjects with a diagnosis of psoriatic arthritis enrolled in Study JPN-02, 12 subjects had joint symptoms at Week 0 and were assessed for pain VAS score (1 subject in the placebo group, 4 subjects in the 45 mg group, 7 subjects in the 90 mg group). In these 12 subjects, the percent improvement in pain VAS score from baseline to Week 12 was -2.8% in the 1 subject in the placebo group and the median values (mean ± SD) in the 45 mg and 90 mg groups were 53.00% (27.19 ± 78.451) and 41.67% (29.88 ± 40.205), respectively. Though the number of subjects assessed was limited, like the results from 22 subjects with joint symptoms, these results have suggested that ustekinumab improves joint pain.

PMDA considers as follows:

As there are a limited number of patients with psoriatic arthritis in Japan, it is understandable that it was difficult to conduct a Japanese clinical study to confirm the efficacy of ustekinumab in reducing joint symptoms. Meanwhile, Japanese Study JPN-02 should have been designed to allow for certain assessment of joint symptoms as well. For example, patients diagnosed with psoriatic arthritis should have been enrolled in the study and balanced across treatment groups for assessment of joint symptoms and the ACR response rates etc. should have also been assessed with a view to comparison with foreign study data. On the other hand, the results from a foreign phase II study, though not a confirmatory study, have suggested the efficacy of ustekinumab in reducing joint symptoms as assessed by the ACR criteria, the results from Japanese Study JPN-02 have shown a trend toward improvement in pain VAS score though in a small number of subjects, and foreign clinical studies of ustekinumab and existing biologics have suggested similar trends in the ACR 20 response rate and pain VAS score. Taking account of these findings, the efficacy of ustekinumab in reducing joint symptoms can be expected also in Japanese patients with psoriatic arthritis and there should be no major problems in the assessment of joint symptoms in the Japanese clinical study. However, as data in Japanese patients with psoriatic arthritis are very limited, data concerning joint symptoms should be obtained wherever possible via post-marketing surveillance, arranging for patients who have mainly joint symptoms and see rheumatologists etc. to be assessed also for disease activity as measured by the ACR core set or DAS, and the information including foreign data on the inhibition of structural damage progression etc., which will become available in future, should be provided appropriately to healthcare providers in clinical settings.

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4.(ii).B.(2) Dosage and administration

4.(ii).B.(2).1) Dosage and administration

4.(ii).B.(2).1).(a) Usual dose

In Japanese Study JPN-02, although the primary endpoint of the PASI 75 response rate at Week 12 tended to be higher in the 90 mg group (67.7%) compared to the 45 mg group (59.4%), the PASI 50 response rate was almost the same in the 45 mg group (82.8%) and the 90 mg group (83.9%), which indicated that both dose levels of ustekinumab can achieve clinically significant improvement in skin lesions in most patients, etc. Thus, a usual dose of 45 mg of ustekinumab has been proposed.

PMDA concluded that there is no particular problem with the proposed usual dose of 45 mg of ustekinumab, which can be expected to produce a clinical response in most psoriasis patients.

4.(ii).B.(2).1).(b) An increased dose of 90 mg

In Foreign Studies T08 and T09, serum ustekinumab concentrations decreased with increasing body weight and the PASI 75 response rate also tended to be lower, and there were differences in efficacy between the 45 mg and 90 mg groups in subjects weighing >100 kg, and the PASI 75 response rate and the trough serum concentration of ustekinumab, etc. in subjects weighing >100 kg in the 90 mg group were comparable to those in subjects weighing ≤100 kg in the 45 mg group. On the basis of these findings, among others, in foreign countries including the US and the EU, the recommended dose of ustekinumab is 45 mg for psoriasis patients weighing ≤100 kg and 90 mg for psoriasis patients weighing >100 kg. Also in Japanese Study JPN-02, serum ustekinumab concentrations decreased with increasing body weight and the PASI 75 response rate also tended to be lower, suggesting that subjects weighing >100 kg tended to have lower serum ustekinumab concentrations. The pharmacokinetics of ustekinumab are considered similar between Japanese and foreign patients of the same body weight range and it is predicted that a dose response relationship as seen in the foreign studies occurs in subjects weighing >100 kg. Therefore, also in Japan, the following statement has been included in the proposed dosage and administration section: “A 90 mg dose may be used in patients weighing >100 kg”.

However, only 6 subjects weighing >100 kg were enrolled in the Japanese study and there is no sufficient evidence supporting the use of a 90 mg dose in this patient population. In addition, Japanese patients weighing >100 kg are uncommon. Taking account of these points, PMDA considers that the proposed dosing instruction is not appropriate.

On the other hand, in Japanese Study JPN-02, the PASI 75 response rate and PASI 90 response rate at Week 12 in the 90 mg group were 8.3% and 10.7% higher, respectively, than those in the 45 mg group and ≥10% higher response rates were observed consistently also after Week 28 and there were no major differences in safety between the two groups. Furthermore, in Study JPN-02 (at Week 28), 33.3% of subjects in the 45 mg group and 17.5% of subjects in the 90 mg group had trough serum ustekinumab concentrations less than the lower limit of quantification (0.17 μg/mL) and this

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proportion was rather high, especially in the 45 mg group, and the PASI 75 response rate in subjects with trough serum ustekinumab concentrations less than the lower limit of quantification was approximately 30% lower than that in subjects with trough serum ustekinumab concentrations of ≥0.17 μg/mL to <0.40 μg/mL [see "4.(i) Summary of clinical pharmacology studies"]. Taking account of these findings, the lack of efficacy in a certain number of subjects due to insufficient serum ustekinumab concentrations is expected at a dose of 45 mg, regardless of body weight (>100 kg). Therefore, in Japan, a dose increase should be recommended as follows: "If the effect of a 45 mg dose is insufficient, a dose of 90 mg may be used."

Since a dose increase may be attempted also in nonresponders to ustekinumab, etc., symptoms over time after the dose increase should be monitored closely and it is necessary to adequately advise against continuing high-dose ustekinumab without careful consideration in patients in whom no effects of the increased dose of ustekinumab are noted. The efficacy and safety of an increased dose of ustekinumab need to be fully investigated via post-marketing surveillance.

4.(ii).B.(2).2) Possibility of withdrawal from ustekinumab therapy etc. after remission

PMDA asked the applicant to explain their view on the possibility of withdrawal of therapy after remission with ustekinumab or the possibility of intermittent administration (treatment interruption with reintroduction as needed) etc.

The applicant explained as follows:

In Foreign Study T08, (a) responders at Week 40 (subjects with a ≥75% improvement in PASI score) were re-randomized to maintenance therapy or withdrawal of therapy and the time to loss of PASI 75 response was assessed. In subjects re-randomized to withdrawal of therapy, the PASI 75 response rate decreased over time and was 63% at Week 52 (12 weeks after treatment withdrawal) and 70.3% of the subjects had an increase in PGA score of ≥1 at Week 52 and (b) furthermore, the percent improvement in PASI score over time after treatment withdrawal in responders at Week 40 re-randomized to placebo (i.e. treatment withdrawal) was assessed according to the percent improvement in PASI score at Week 40 (≥75% to <90% [32 subjects in the 45 mg group, 45 subjects in the 90 mg group] vs. ≥90% [109 subjects in the 45 mg group, 134 subjects in the 90 mg group]). The mean and median percent improvements in PASI scores were less than 75% at Weeks 48 to 52 in subjects with a ≥75% to <90% improvement at Week 40 and less than 75% at Week 60 even in subjects with a ≥90% improvement at Week 40, suggesting that it is not true that PASI response is maintained for a long time in subjects who showed a higher percent improvement in PASI score. Based on these results, continuous administration of ustekinumab is recommended.

PMDA considers as follows:

Given that ustekinumab is associated with the risk of serious adverse reactions, the amount of ustekinumab used should be minimized. As patients with prolonged remission etc. may be studied, a more detailed investigation concerning treatment withdrawal and intermittent administration as needed

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etc. should be performed in future. It is important to investigate symptoms over time etc. in patients after treatment withdrawal and patients retreated after withdrawal from therapy etc. and collect sufficient information, also after the product launch.

4.(ii).B.(3) Indications and clinical positioning etc.

4.(ii).B.(3).1) Indications

PMDA considers as follows:

The confirmatory study of ustekinumab was designed to enrollpatients regardless of prior medication use, etc. and was conducted on the assumption that ustekinumab would be used even as a first-line drug for patients resistant to local therapy (i.e. as an equal option to phototherapy or conventional systemic therapy such as cyclosporine and etretinate). Psoriasis is not generally a fatal disease while ustekinumab, as with adalimumab and infliximab (other biologics approved for psoriasis), increases the risk of serious infections etc. which may run a fatal course, and the long-term safety of ustekinumab including the risk of malignancy has not fully been elucidated. Taking account of these points, it is not appropriate to position ustekinumab as an equal option to phototherapy or conventional systemic therapy and ustekinumab should rather be positioned as a treatment, like the approved biologics, for patients who have had an inadequate response or intolerance to phototherapy or conventional systemic therapy, etc.

PMDA asked the applicant to present the results of subgroup analyses of patients who were considered to have an inadequate response to phototherapy or cyclosporine or etretinate. As described below, the applicant responded that there were no major differences in the efficacy and safety of ustekinumab between the subgroups and the overall population.

Although the response to prior therapy for psoriasis was not reported in Japanese Study JPN-02, given that the study included patients with moderate to severe psoriasis, it is inferred that the majority of the subjects failed to respond adequately to prior therapy. Thus, subgroup analyses were performed according to previous experience with cyclosporine, etretinate or phototherapy. As a result, regarding efficacy, the PASI 75 response rates among subjects with previous experience with cyclosporine, etretinate, or phototherapy were 59.6% (31 of 52 subjects) in the 45 mg group, 67.2% (39 of 58 subjects) in the 90 mg group, and 0% (0 of 25 subjects) in the placebo group, which were almost comparable to those in the overall population (59.4% in the 45 mg group, 67.7% in the 90 mg group, 6.5% in the placebo group). Also when subgroups were analyzed according to previous experience with each of cyclosporine, etretinate, and phototherapy, there were no major differences in the results between each of the subgroups and the overall population, though the number of subjects of each subgroup was small. Regarding safety, overall adverse events, serious adverse events, adverse events leading to treatment discontinuation, and serious infections were analyzed according to previous experience with each of cyclosporine, etretinate, and phototherapy. As a result, the incidences of adverse events by treatment group were similar, regardless of previous experience with each of these therapies.

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Furthermore, as the response to prior therapy was reported in Foreign Studies T08 and T09, a subgroup analysis of subjects who had an inadequate response to cyclosporine, acitretin (an oral retinoid, unapproved in Japan), or phototherapy was performed. The PASI 75 response rates at Week 12 in the 45 mg, 90 mg, and placebo groups were 66.8% (181 of 271 subjects), 70.1% (162 of 231 subjects), and 2.2% (6 of 267 subjects), respectively, which were almost comparable to those in the overall population (66.9% in the 45 mg group, 72.1% in the 90 mg group, 3.5% in the placebo group). There were also no major differences in safety between the subgroup of subjects who had an inadequate response to cyclosporine, acitretin, or phototherapy and the overall population.

Based on the above, PMDA considers as follows:
The indication statement should be modified as shown below and the following statements should be included in the precautions for indications section of the package insert: ustekinumab should be used in (a) patients with a body surface area involvement of ≥10% who have had an inadequate response to conventional systemic therapy (including UV-light therapy) or (b) patients with refractory skin or joint symptoms. In addition, the use of ustekinumab should be limited to physicians who are familiar with the diagnosis and treatment of psoriasis to ensure that a correct diagnosis is made, that appropriate patients are selected, and that the proper use is complied with.

[Indications]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris, Psoriatic arthritis

Given that ustekinumab has been demonstrated to be highly effective in the treatment of plaque psoriasis etc. and that its mechanism of action is different from conventional therapy, ustekinumab is expected to play an important role in the treatment of psoriasis. In order to prevent ustekinumab from being used improperly, it is important that the use of ustekinumab is determined carefully based on its risks and benefits and that patients themselves also fully understand the risks of ustekinumab and comply with its proper use.

4.(ii).B.(3).2) Positioning of ustekinumab relative to existing biologics
While both adalimumab and infliximab (other biologics approved for the treatment of psoriasis) neutralize the biological activity of human TNF-α, ustekinumab binds to human IL-12 and IL-23 and neutralizes their biological activities. Ustekinumab has a novel mechanism of action. PMDA asked the applicant to explain their view on the positioning of ustekinumab relative to the existing biologics.

The applicant explained as follows:
No head to head efficacy studies of ustekinumab vs. adalimumab or infliximab have been performed in Japan or overseas.Adalimumab and infliximab were approved for the indication of psoriasis in

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Japan in January 2010 and there is limited clinical experience with these biologics in Japanese psoriasis patients at present. Thus, it is difficult to define the positioning of ustekinumab relative to these drugs. Compared to these drugs, ustekinumab has the following characteristics: (a) Comparison of the results of Japanese clinical studies indicates that the efficacy of ustekinumab in treating psoriatic skin lesions is as high as that of adalimumab or infliximab (Table 27), (b) The safety databases, which include Japanese and foreign data, have shown a favorable safety profile of ustekinumab and there should be no particular safety concerns about ustekinumab compared to anti-TNF agents at present, and (c) Psoriasis has a chronic nature, which often requires long-term treatment, while the effect of ustekinumab is maintained by subcutaneous injections every 12 weeks and ustekinumab requires lower dosing frequency and is easier to use, compared to adalimumab and infliximab. Furthermore, ustekinumab has a novel mechanism of action and the results from foreign phase III studies have suggested the efficacy of ustekinumab also in subjects who have discontinued other biologic therapy due to an inadequate response. There have been no safety concerns about the use of ustekinumab, even in subjects who have discontinued other biologic therapy due to intolerance (Tables 28 and 29). Taking account of these findings, ustekinumab is expected to possibly offer another therapeutic option for patients who do not respond to adalimumab or infliximab or those who cannot use adalimumab or infliximab for safety reasons.

Table 27. Comparison of efficacy of ustekinumab vs. other biologics
based on Japanese placebo-controlled, double-blind studies in psoriasis patients

Non-proprietary name	Ustekinumab		Adalimumab[a]		Infliximab[a]	
Psoriasis severity	PASI ≥12 BSA ≥10%		PASI ≥12 BSA ≥10%		PASI ≥12 BSA ≥10%	
Dosing regimen during the placebo-controlled period	45 mg, 90 mg, or placebo administered at Weeks 0 and 4		40 mg, 80 mg, or placebo administered every other week (including loading dose of 80 mg followed by 40 mg given every other week)		5 mg/kg or placebo intravenously administered at Weeks 0, 2, and 6	
Primary endpoint	PASI 75 response rate at Week 12		PASI 75 response rate at Week 16		PASI 75 response rate at Week 10	
PASI 75 response rate at the proposed or approved dosing regimen	Placebo	45 mg	Placebo	80 mg loading dose + 40 mg	Placebo	5 mg/kg
	6.5% (2/31 subjects)	59.4% (38/64 subjects)	4.3% (2/46 subjects)	62.8% (27/43 subjects)	0% (0/19 subjects)	68.6% (24/35 subjects)

a: Cited from the disclosed CTD and the package insert

Table 28. PASI 50, PASI 75, and PASI 90 response rates (Week 12) in subjects previously treated with other biologics

	Pooled data from Studies T08 and T09		
	Placebo	45 mg	90 mg
Patients who have discontinued other biologic therapy (etanercept, infliximab, adalimumab, alefacept, efalizumab) due to an inadequate response (n)	104	81	106
PASI 90 response rate	1 (1.0%)	32 (39.5%)	38 (35.8%)
PASI 75 response rate	2 (1.9%)	47 (58.0%)	70 (66.0%)
PASI 50 response rate	7 (6.7%)	63 (77.8%)	86 (81.1%)

n (%)

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Table 29. Overview of adverse events in subjects who inadequately responded to or were intolerant to other biologic therapies (through Week 12) (Pooled data from Studies T08 and T09)

	Overall population			Patients who inadequately responded to other biologic therapies			Patients who were intolerant to other biologic therapies		
Treatment group	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
No. of patients treated	665	664	666	104	81	106	25	21	26
Mean evaluation period (weeks)	12.0	12.2	12.2	11.9	12.2	12.2	12.3	12.2	12.1
Patients with adverse events	324 (48.7)	361 (54.4)	328 (49.2)	54 (51.9)	40 (49.4)	56 (52.8)	14 (56.0)	14 (66.7)	13 (50.0)
Patients with serious adverse events	10 (1.5)	10 (1.5)	9 (1.4)	0 (0.0)	1 (1.2)	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with adverse events leading to treatment discontinuation	13 (2.0)	2 (0.3)	10 (1.5)	4 (3.8)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious infections	3 (0.5)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (%)

PMDA considers as follows:

Although there is no objection to the applicant's view that the efficacy of ustekinumab in treating psoriatic skin lesions is as high as that of adalimumab or infliximab, the effect on joint symptoms is also important when considering the positioning of different biologics in the treatment of psoriasis and the positioning of ustekinumab needs to be further discussed, taking also account of the data on its effect in preventing the progression of joint damage, etc., which will be obtained from foreign studies. Regarding safety, as there is limited clinical experience with ustekinumab in Japan and overseas, it is necessary to collect sufficient information via post-marketing surveillance etc. and then determine the risk-benefit balance of ustekinumab and the consequent positioning of ustekinumab. Based on the novel mechanism of action of ustekinumab and foreign data, ustekinumab is expected to be useful also in patients who have responded inadequately to existing biologics. However, as no relevant Japanese data are available, it is necessary to investigate it via post-marketing surveillance etc. and provide the information to healthcare providers in clinical settings. On the other hand, the efficacy of other biologics in patients who have responded inadequately to ustekinumab has not so far been studied overseas or in Japan and such data will also be important for defining the positioning of biologics (choice between different biologics) and this is an issue for a future investigation.

4.(ii).B.(3).3) Concomitant use with conventional systemic therapy and switching from other biologics to ustekinumab

PMDA considers as follows:

Although it is envisaged that ustekinumab may be used in combination with systemic therapy such as cyclosporine and etretinate or phototherapy for refractory cases etc., there are no sufficient data regarding these combinations. Especially, when ustekinumab is used in combination with immunosuppressive systemic therapy, the possibility of developing infections or malignancies due to enhanced immunosuppression cannot be ruled out, and when ustekinumab is used in combination with phototherapy, the possibility of an increased risk of skin cancer cannot be excluded either. Thus, the package insert etc. should advise that the safety of ustekinumab in combination with other systemic therapy or phototherapy has not been established, so that the risks and benefits of such combination therapy will be determined carefully after consideration of the safety of each therapy.

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Although there is no specific evidence about the concomitant use of ustekinumab with other biologics that affect the immune system, it is desiable to avoid the use of ustekinumab in combination with other biologics, as it has been reported that the use of a combination of different biologics resulted in an increased incidence of serious infections in patients with rheumatoid arthritis. Likewise, also when switching from other biologics to ustekinumab is carried out, adequate caution should be exercised against the possible development of serious infections etc. and such precaution statement should also be included in the package insert etc.

Furthermore, it is necessary to carefully investigate, also in the post-marketing surveillance, the actual state of concomitant use with systemic therapy or phototherapy (proportion, patient background, duration of concomitant use, etc.), the safety and efficacy of the concomitant use, the actual state of switching from other biologics (proportion, patient background, washout period, etc.), and the safety and efficacy of the switching to ustekinumab, etc., and provide the obtained information to medical practice as appropriate to promote the proper use of ustekinumab.

4.(ii).B.(4) Safety

4.(ii).B.(4).1) Overview of safety

Adverse events during the placebo-controlled period through Week 12 and during the treatment period through Week 72 in Japanese Study JPN-02, and during the placebo-controlled period through Week 12 and during the entire reporting period in pooled 3 foreign psoriasis studies (T04, T08, T09) are summarized in Table 30 and Table 31, respectively.

Table 30. Adverse events in Japanese study

	Study JPN-02			
	(Through Week 12)			(Through Week 72)
	Ustekinumab		Placebo (N = 32)	Combined ustekinumab (N = 154)
	45 mg (N = 64)	90 mg (N = 62)		
Deaths	0	0	0	0
Serious adverse events	0	3 (4.8)	2 (6.3)	13 (8.4)
Serious adverse events leading to treatment discontinuation	0	3 (4.8)	1 (3.1)	6 (3.9)
Serious adverse events related to study drug	0	3 (4.8)	1 (3.1)	8 (5.2)
All adverse events	42 (65.6)	37 (59.7)	21 (65.6)	150 (97.4)
Adverse events leading to treatment discontinuation	0	4 (6.5)	2 (6.3)	6 (3.9)
Adverse events related to study drug	35 (54.7)	28 (45.2)	19 (59.4)	136 (88.3)

n (%)

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Table 31. Adverse events in pooled 3 foreign psoriasis studies

	Studies T04, T08, and T09				
	Through Week 12				Entire reporting period [a]
	Ustekinumab			Placebo (N = 732)	Combined ustekinumab (N = 2266)
	45 mg (N = 790)	90 mg (N = 792)	Combined ustekinumab (N = 1582)		
Deaths	0	1 (0.1)	1 (0.1)	0	1 (0.04)
Serious adverse events	13 (1.6)	11 (1.4)	24 (1.5)	10 (1.4)	75 (3.3)
All adverse events	455 (57.6)	409 (51.6)	864 (54.6)	369 (50.4)	1676 (74.0)
Adverse events leading to treatment discontinuation	9 (1.1)	11 (1.4)	20 (1.3)	14 (1.9)	57 (2.5)

n (%)
a: Data through Week 36 from Study T04, data through Week 52 from Study T08, and data through Week 28 from Study T09 were pooled for the table.

In Japanese Study JPN-02, there were no major differences in the incidence of adverse events during the placebo-controlled period through Week 12 among the placebo, 45 mg, and 90 mg groups and the incidence of adverse events through Week 72 was also similar between the 45 mg and 90 mg groups. The system organ class (SOC) with the highest incidence of adverse events during the placebo-controlled period in either of the ustekinumab groups was “Investigations” (18.8% [6 of 32 subjects] in the placebo group, 29.7% [19 of 64 subjects] in the 45 mg group, 22.6% [14 of 62 subjects] in the 90 mg group), followed by “Infections and infestations” (18.8% [6 of 32 subjects] in the placebo group, 20.3% [13 of 64 subjects] in the 45 mg group, 24.2% [15 of 62 subjects] in the 90 mg group) and common adverse events (≥5%) in either of the ustekinumab groups were nasopharyngitis (9.4% [3 of 32 subjects] in the placebo group, 15.6% [10 of 64 subjects] in the 45 mg group, 16.1% [10 of 62 subjects] in the 90 mg group), blood triglycerides increased (3.1% [1 of 32 subjects] in the placebo group, 10.9% [7 of 64 subjects] in the 45 mg group, 0% [0 of 62 subjects] in the 90 mg group), and eosinophil count increased (3.1% [1 of 32 subjects] in the placebo group, 4.7% [3 of 64 subjects] in the 45 mg group, 6.5% [4 of 62 subjects] in the 90 mg group). The SOC with the highest incidence of adverse events through Week 72 in the combined ustekinumab group was “Infections and infestations” (68.8% [106 of 154 subjects]). No deaths were reported. The incidences of serious adverse events during the placebo-controlled period were 6.3% (2 of 32 subjects) in the placebo group, 0% (0 of 64 subjects) in the 45 mg group, and 4.8% (3 of 62 subjects) in the 90 mg group and no consistent trend was observed and serious adverse events reported by ≥2 ustekinumab-treated subjects through Week 72 were cataract (1 subject each in the 45 mg and 90 mg groups) and fall (1 subject each in the 45 mg and 90 mg groups).

In pooled 3 foreign psoriasis studies, there were no major differences in the incidence of adverse events during the placebo-controlled period through Week 12 among the placebo, 45 mg, and 90 mg groups and the incidence of adverse events during the entire reporting period was also similar between the 45 mg and 90 mg groups and between the placebo→45 mg and placebo→90 mg groups. The SOC with the highest incidence of adverse events during the placebo-controlled period was “Infections and infestations” for all groups (22.8% [167 of 732 subjects] in the placebo group, 26.3% [208 of 790 subjects] in the 45 mg group, 24.9% [197 of 792 subjects] in the 90 mg group) and common adverse

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events (≥5%) in either of the ustekinumab groups were nasopharyngitis (7.9% [58 of 732 subjects] in the placebo group, 8.4% [66 of 790 subjects] in the 45 mg group, 8.0% [63 of 792 subjects] in the 90 mg group), headache (4.5% [33 of 732 subjects] in the placebo group, 5.7% [45 of 790 subjects] in the 45 mg group, 5.9% [47 of 792 subjects] in the 90 mg group), and upper respiratory tract infection (4.4% [32 of 732 subjects] in the placebo group, 5.7% [45 of 790 subjects] in the 45 mg group, 5.2% [41 of 792 subjects] in the 90 mg group). No major differences in the nature or incidence of adverse events were observed between the entire reporting period and the placebo-controlled period and the nature and incidence of adverse events were similar also between the two doses. Sudden cardiac death considered due to congestive cardiomyopathy occurred in 1 subject randomized to the 90 mg group in Study T09. The incidence of serious adverse events during the placebo-controlled period was similar among the treatment groups and the SOCs with the highest incidence of serious adverse events in either of the ustekinumab groups were "Cardiac disorders" (0% [0 of 732 subjects] in the placebo group, 0.1% [1 of 790 subjects] in the 45 mg group, 0.5% [4 of 792 subjects] in the 90 mg group) and "Infections and infestations" (0.4% [3 of 732 subjects] in the placebo group, 0% [0 of 790 subjects] in the 45 mg group, 0.5% [4 of 792 subjects] in the 90 mg group). There were no major differences either in the incidence of serious adverse events during the entire reporting period between the two doses and the SOCs with the highest incidence of serious adverse events in the combined ustekinumab group were "Cardiac disorders" (0.7% [15 of 2266 subjects]) and "Infections and infestations" (0.7% [15 of 2266 subjects]), which were the same as those during the placebo-controlled period.

4.(ii).B.(4).2) Significant adverse events

As shown below, the applicant explained about (a) infections, malignancy, and asthma as events theoretically associated with ustekinumab, (b) cardiovascular disorders and psoriasis as events associated with psoriasis that is the primary disease, and (c) allergy and injection site reactions as events associated with ustekinumab as an antibody preparation. PMDA's questions regarding these events and the applicant's responses are also listed below. In this section, adverse events during the entire reporting period in pooled 3 foreign psoriasis studies are based on data through Week 36 from Study T04, data through Week 52 from Study T08, and data through Week 28 from Study T09, as in the above 4.(ii).B.(4).1) Overview of safety.

4.(ii).B.(4).2).(a) Serious infections

Serious infections reported in Japanese Study JPN-02 were pneumonia in 1 subject in the 90 mg group during the placebo-controlled period and pharyngitis in 1 subject and cellulitis in 1 subject after Week 12 through 72. In pooled 3 foreign psoriasis studies, serious infections during the placebo-controlled period through Week 12 and during the entire reporting period were as shown in Table 32 and Table 33, respectively, and the event reported by ≥2 subjects in any group was cellulitis.

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Table 32. Serious infections in 3 foreign psoriasis studies (Placebo-controlled period through Week 12)

	Ustekinumab			Placebo
	45 mg	90 mg	Combined ustekinumab	
No. of subjects treated	790	792	1582	732
Mean observation period (weeks)	12.2	12.1	12.1	12.0
Mean treatment period (weeks)	4.0	4.0	4.0	4.0
No. of subjects with serious infections	0 (0.0)	4 (0.5)	4 (0.3)	3 (0.4)
Infections and infestations	0 (0.0)	4 (0.5)	4 (0.3)	3 (0.4)
Cellulitis	0 (0.0)	2 (0.3)	2 (0.1)	2 (0.3)
Herpes zoster disseminated	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)

n (%)

Table 33. Serious infections in 3 foreign psoriasis studies (Entire reporting period)

	Ustekinumab			Placebo
	45 mg	90 mg	Combined ustekinumab	
No. of subjects treated [a]	1110	1156	2266	732
Total subject-years of follow-up	725	742	1467	182
Serious infections	6	9	15	3
No. of events per 100 subject-years	0.83	1.21	1.02	1.65
95% CI [b]	(0.30,1.80)	(0.55, 2.30)	(0.57, 1.69)	(0.57,1.69)

a: Placebo-to-ustekinumab crossover subjects were included in the ustekinumab group after crossover to ustekinumab.
b: Confidence interval calculated with Fisher's exact test

In Study T08, 1 subject in the 90 mg group had herpes zoster disseminated, which was a possible opportunistic infection. Although no active tuberculosis was reported in the above Japanese and foreign studies, after the data cutoff dates of these studies, 1 case of presumed reactivation of latent tuberculosis was reported in a phase III psoriasis study (Study T25), which is ongoing in Korea and Taiwan.

According to the latest foreign post-marketing safety data collected between December 31, 2008 (International Birth Date) and August 2, 2010, a total of 37 cases of serious infections were reported and based on cumulative exposure of 18,380 patient-years estimated from the latest PSUR through June 30, 2010, its frequency was considered low. There were no reports of unconventional infections or opportunistic infections etc. and 2 cases of tuberculosis and 4 cases of sepsis were reported, but the reporting rates were low, i.e. 0.01 per 100 patient-years and 0.02 per 100 patient-years, respectively.

Based on the above, although no apparent impact of ustekinumab on infections has been seen to date, as ustekinumab is a selective immunosuppressant and may increase the risk of infections or of exacerbating infections, adequate warning and precaution information will be provided on the package insert: it will be stated in the warnings section that serious infections have been reported and that ustekinumab may increase the risk of reactivation of latent tuberculosis infection, etc. Furthermore, caution statements about infections and tuberculosis will be included in the contraindications and precautions sections as well.

PMDA asked the applicant to discuss the potential for ustekinumab to increase the risk of tuberculosis infection, taking account of its possibility of affecting the expression of TNF-α, etc. and the findings from IL-12- and IL-23-related gene knockout animals, etc.

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The applicant explained as follows:
Based on the results of pharmacodynamic assessments as part of foreign clinical studies in patients with psoriasis, a decrease in mRNA for TNF-α in lesional skin was observed after ustekinumab treatment, which is considered to be associated with recovery of inflammation (Study T01) and serum TNF-α levels were unchanged (Study T04). On the other hand, infection experiments suggested that IL-12- and IL-23-related gene knockout mice and mice treated with neutralizing antibodies to IL-12 and IL-23 had decreased host defense against pathogenic agents including mycobacteria and an increased susceptibility to initial mycobacterial infection in humans with IL-12- and IL-23-related gene deficiency has been reported [see "3.(iii) Summary of toxicology studies"]. However, based on clinical study data and foreign post-marketing safety data, the risk of tuberculosis associated with ustekinumab treatment is not high and it is just a potential risk under the current situation, which can be managed through selection of appropriate patients and the prevention and appropriate treatment of latent tuberculosis, in accordance with the above-mentioned draft package insert.

PMDA considers as follows:
Given that a few cases of tuberculosis have been reported in clinical studies and foreign post-marketing experience and that it has been suggested that IL-12- and IL-23-related gene knockout mice and genetically deficient humans have decreased host defense to mycobacteria, the risk of tuberculosis infection associated with ustekinumab cannot be denied and as proposed by the applicant, adequate warning and precaution information should be provided on the package insert etc. Moreover, it should also be noted that the incidence rate of tuberculosis is higher in Japan than in Europe and the US and the tuberculosis trend should be watched continuously.

Not only tuberculosis but also other serious infections are of greatest concern regarding the safety profile of ustekinumab. It is important to establish the procedures for cooperation between dermatologists who are the main physicians treating psoriasis and specialists who are capable of diagnosing and treating serious infections, in collaboration with the relevant academic societies, and take thorough measures to prevent and detect early adverse drug reactions, etc. [see "4.(ii).B.(5) Post-marketing safety measures"].

4.(ii).B.(4).2).(b) Malignancy
Malignancies reported in Japanese Study JPN-02 were prostate cancer in 1 subject in the 90 mg group during the placebo-controlled period and cervix carcinoma stage 0 in 1 subject after Week 12 through Week 72.

During the placebo-controlled period through Week 12 in pooled 3 foreign psoriasis studies, 2 subjects each in the placebo, 45 mg, and 90 mg groups reported malignancies and the rates of malignancies were 1.13, 0.99, and 0.98 cases per 100 subject-years of follow-up in the placebo, 45 mg, and 90 mg groups, respectively. One of the 2 subjects in the placebo group, 1 of the 2 subjects in the 45 mg group, and 2 of the 2 subjects in the 90 mg group had non-melanoma skin cancer and the rates of

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non-melanoma skin cancer were 0.57, 0.49, and 0.98 cases per 100 subject-years of follow-up in the placebo, 45 mg, and 90 mg groups, respectively. During the entire reporting period, 19 subjects in the combined ustekinumab group reported malignancies and the rate of malignancies in the combined ustekinumab group was 1.30 cases per 100 subject-years of follow-up. Of the 19 subjects, 14 subjects had non-melanoma skin cancer and the rate of non-melanoma skin cancer was 0.96 cases per 100 subject-years of follow-up. Malignancies other than non-melanoma skin cancer in the remaining 5 subjects were prostate cancer (2 subjects), breast cancer (1 subject), renal cancer (1 subject), and thyroid cancer (1 subject) and no consistent trend was observed. When the number of ustekinumab-treated subjects with malignancies other than non-melanoma skin cancer during the entire reporting period (5 cases) was compared with what would be expected in the general US population according to the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) database (7.05 cases), the standardized incidence ratio (the ratio of the observed-to-expected number of cases) and its 95% confidence interval were 0.71 [0.23,1.65] and no major differences were observed. When the rate of non-melanoma skin cancer cases per 100 subject-years of follow-up was compared between clinical studies of ustekinumab vs. other biologics, as shown in Table 34, the rate in the combined ustekinumab group was similar to those with 3 other biologics.

Table 34. Comparison of the rates of non-melanoma skin cancer with ustekinumab vs. other biologics

	Ustekinumab [a]	Infliximab [b]	Efalizumab [c]	Etanercept [d]
Total subject-years of follow-up [e]	1463	1101	1784	1062
Observed number of cases	14	17	20	12
No. of cases per 100 subject-years	0.96	1.54	1.12	1.13
95% CI [f]	(0.52, 1.61)	(0.90, 2.47)	(0.68, 1.73)	(0.58, 1.97)

a: Data from 3 foreign psoriasis studies
b: Data from foreign phase II and III clinical studies (Centocor's internal documents)
c: Unapproved in Japan. Data from The Dermatologic and Ophthalmic Drugs Advisory Committee, FDA [September 9, 2003, RAPTIVA™ (efalizumab)]
d: Unapproved for treatment of psoriasis in Japan. Enbrel (BLA 103795) data at the time of US approval.
e: Non-melanoma skin cancer includes basal cell carcinoma and squamous cell carcinoma.
f: Confidence interval calculated with Fisher's exact test

Eight cases of malignancies were collected from the latest foreign post-marketing safety data and except for prostate cancer reported by 3 patients, all malignancies were each reported by only 1 patient (anaplastic large cell lymphoma T- and null-cell types, breast cancer, gallbladder cancer, pancreatic carcinoma, renal cancer).

Based on the above, although no apparent impact of ustekinumab on malignancy has been seen to date, as ustekinumab is a selective immunosuppressant and may increase the risk of malignancy, the warning and precaution information concerning malignancy will be included in the warnings and precautions sections of the package insert, as in the case of other biologics.

PMDA considers as follows:
Although a causal relationship between ustekinumab and malignancy is not clear at present, as in the case of other biologics, the possibility that ustekinumab affects the host defense to malignant tumors cannot be denied and it is necessary to continue to conduct a large-scale, long-term investigation of the

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relationship between ustekinumab and malignancy. Generally, psoriasis patients have previously experienced phototherapy or immunosuppressants and are particularly susceptible to non-melanoma skin cancer. Therefore, it is necessary to collect post-marketing information on the occurrence of non-melanoma skin cancer in psoriasis patients and the background of patients with non-melanoma skin cancer, etc. and investigate their relationship to ustekinumab in details.

4.(ii).B.(4).2).(c) Asthma

As ustekinumab inhibits Th1 cell differentiation, it is theoretically possible that ustekinumab shifts the immune response toward a Th2 phenotype and exacerbates atopic diseases. Thus, the effects of ustekinumab on asthma were investigated.

In Japanese Study JPN-02, asthma was reported by 1 subject in the 45 mg group (1.6%) and 1 subject in the 90 mg group (1.6%), but not in the placebo group. Both events were mild in severity and both subjects with asthma had prior or concurrent bronchial asthma.

In pooled 3 foreign psoriasis studies, the incidences of asthma during the placebo-controlled period through Week 12 were 0.1% (1 of 732 subjects) in the placebo group, 0% (0 of 790 subjects) in the 45 mg group, and 0.5% (4 of 792 subjects) in the 90 mg group and the incidence during the entire reporting period in the combined ustekinumab group was 0.5% (11 of 2266 subjects). No serious adverse events related to asthma were observed in ustekinumab-treated subjects and serious asthma exacerbation occurred in 1 subject in the placebo group. There were no treatment discontinuations due to asthma. While 22.5% (450 of 1996 subjects) or 1.2% (23 of 1996 subjects) of subjects enrolled in Studies T08 and T09 had prior/concurrent seasonal allergy or atopic dermatitis, respectively (this information not collected in Study T04), the incidence of seasonal allergy during the entire reporting period in the combined ustekinumab group was 0.5% (11 of 2266 subjects) and atopic dermatitis was not reported.

Based on the above, treatment with ustekinumab is unlikely to significantly affect Th2-mediated diseases such as asthma or other atopic diseases.

PMDA considers as follows:

Although there is no objection to the applicant’s view that ustekinumab has no significant effects on Th2-mediated diseases based on the currently available information, severe asthma patients were excluded from the clinical studies and there is limited clinical experience with ustekinumab in patients with concurrent atopic dermatitis etc. Thus, it is necessary to investigate the effects of ustekinumab on these diseases in more details via post-marketing surveillance and to appropriately provide the obtained information (e.g. ustekinumab has a theoretical risk of exacerbating Th2-mediated diseases) to healthcare providers in clinical settings.

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4.(ii).B.(4).2).(d) Cardiovascular disorder

It has been reported that the risk of occlusive vascular diseases such as myocardial infarction and stroke is increased in psoriasis patients, which is considered attributable to a high prevalence, among the patients, of cardiovascular risk factors such as hypertension, hyperlipidaemia, diabetes mellitus, obesity, and smoking. Also, psoriasis itself has been reported to be a cardiovascular risk factor. Thus, as a risk to the psoriasis patient population, the impact of ustekinumab on cardiovascular adverse events was assessed.

In Japanese Study JPN-02, events classified as "cardiac disorders" or "vascular disorders" were assessed. The incidences of cardiac disorders during the placebo-controlled period were 3.1% (1 of 32 subjects, cardiac failure congestive) in the placebo group, 1.6% (1 of 64 subjects, supraventricular extrasystoles) in the 45 mg group, and 0% (0 of 62 subjects) in the 90 mg group and the incidence through Week 72 in the combined ustekinumab group was 5.8% (9 of 154 subjects, ventricular extrasystoles [5 subjects], supraventricular extrasystoles [1 subject], arrhythmia [1 subject], and left ventricular hypertrophy [1 subject], in addition to the above). The incidences of vascular disorders during the placebo-controlled period were 3.1% (1 of 32 subjects, hypertension) in the placebo group, 0% (0 of 64 subjects) in the 45 mg group, and 1.6% (1 of 62 subjects, thrombosis) in the 90 mg group and the incidence through Week 72 in the combined ustekinumab group was 5.8% (9 of 154 subjects, hypertension [7 subjects] and arteriosclerosis [1 subject], in addition to the above). The events observed in ustekinumab-treated subjects were all mild in severity.

In pooled 3 foreign psoriasis studies, the overall incidence of cardiovascular adverse events during the placebo-controlled period through Week 12 was similar for all groups, i.e. 4.5% (33 of 732 subjects) in the placebo group, 3.8% (30 of 790 subjects) in the 45 mg group, and 4.4% (35 of 792 subjects) in the 90 mg group. The overall incidences of cardiovascular adverse events during the entire reporting period were 9.2% (73 of 790 subjects) in the 45 mg group, 9.8% (78 of 792 subjects) in the 90 mg group, 6.3% (20 of 320 subjects) in the placebo→45 mg group, and 3.3% (12 of 364 subjects) in the placebo→90 mg group, and there was no increase in incidence with increasing dose.

As serious cardiovascular adverse events, objective events of "serious myocardial infarction", "serious stroke", and "cardiovascular death" were identified and assessed. As a result, 5 serious cardiovascular adverse events occurred in ustekinumab-treated subjects only during the placebo-controlled period (2 events in the 45 mg group, 3 events in the 90 mg group) and the rates were 0 events per 100 subject-years in the placebo group, 0.98 events per 100 subject-years in the 45 mg group, and 1.47 events per 100 subject-years in the 90 mg group. The rates during the entire reporting period were 0.55 events per 100 subject-years in the placebo group (since myocardial infarction [1 subject] occurred during the follow-up period after study drug discontinuation, this event was analyzed as occurring during the entire reporting period, instead of during the placebo-controlled period) and 0.61 events per 100 subject-years in the combined ustekinumab group. When "serious ischaemic events" were assessed as serious cardiovascular adverse events, the rates during the placebo-controlled period were

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0 events per 100 subject-years in the placebo group, 1.48 events per 100 subject-years in the 45 mg group, and 1.47 events per 100 subject-years in the 90 mg group and the rates during the entire reporting period were 0.55 events per 100 subject-years in the placebo group and 0.95 events per 100 subject-years in the combined ustekinumab group.

Based on the above, it was considered that there was no apparent trend of increased cardiovascular risk associated with ustekinumab.

PMDA asked the applicant to explain their view on the appropriateness of the use of ustekinumab in psoriasis patients with severe cardiovascular disease.

The applicant explained as follows:
Although patients with stable cardiovascular disease were not excluded from Foreign Studies T08 and T09 and 5.6% of the subjects had myocardial infarction, coronary artery bypass, stroke, transient ischaemic attack, or atherosclerotic cardiovascular disease at baseline, as these clinical studies showed no apparent trend of increased cardiovascular risk associated with ustekinumab, there should be no problem with the use of ustekinumab even in patients with concurrent severe cardiovascular disease as long as they are appropriately managed by physicians and their symptoms are stable.

PMDA considers as follows:
Since there are no findings suggestive of increased cardiovascular risk in IL-12- and IL-23-related gene knockout animals and genetically deficient humans, at present, there is no need to restrict the use of ustekinumab in patients with cardiovascular disease including those with severe disease. However, as there is limited clinical experience with ustekinumab in these patients in the clinical studies, it is necessary to continue to carefully investigate the effects of ustekinumab on the cardiovascular system via post-marketing surveillance etc.

4.(ii).B.(4).2).(e) Psoriasis
In order to assess the effects of ustekinumab on psoriasis rebound, psoriasis-related adverse events and psoriasis rebound after stopping therapy were investigated.

In Japanese Study JPN-02, the incidences of psoriasis-related adverse events during the placebo-controlled period were 25.0% (8 of 32 subjects) in the placebo group, 1.6% (1 of 64 subjects) in the 45 mg group, and 4.8% (3 of 62 subjects) in the 90 mg group, and the incidence was lower in ustekinumab-treated subjects compared to placebo-treated subjects. The incidence through Week 72 in the combined ustekinumab group was 5.2% (8 of 154 subjects).

In pooled 3 foreign psoriasis studies, the incidences of psoriasis-related adverse events during the placebo-controlled period through Week 12 were 2.3% (17 of 732 subjects) in the placebo group, 0.4% (3 of 790 subjects) in the 45 mg group, and 1.4% (11 of 792 subjects) in the 90 mg group, and

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the incidence was lower in ustekinumab-treated subjects compared to placebo-treated subjects. The incidence during the entire reporting period in the combined ustekinumab group was 1.2% (27 of 2266 subjects).

Psoriasis rebound was evaluated in Studies T04 and T08 where evaluation was continued also after stopping ustekinumab therapy. Rebound was defined as the occurrence of new erythrodermic or pustular psoriasis or exacerbation of psoriasis to ≥125% of the baseline PASI within 3 months after the last dose of ustekinumab. In Study T04, 2 subjects had PASI ≥125% of baseline. In Study T08, the criteria for rebound were not fulfilled between the last dose and Week 40 for any subject in the treatment withdrawal group.

Based on the above, no important findings were observed regarding the effects of ustekinumab on psoriasis-related events and psoriasis rebound after stopping therapy.

As exacerbation and new onset of psoriasis have been reported with anti-TNF agents and a relevant precautionary statement is included in the package insert, PMDA asked the applicant to present the occurrence of psoriasis in non-psoriasis clinical studies of ustekinumab and then explain whether a similar precautionary statement is necessary also for ustekinumab.

The applicant explained as follows:
In addition to psoriasis clinical studies, multiple sclerosis and Crohn's disease clinical studies were conducted overseas and a total of 336 subjects received ustekinumab. In these clinical studies, serious psoriasis was not reported and non-serious psoriasis was reported by 1 patient with Crohn's disease, but the patient had a history of psoriasis and its causal relationship to ustekinumab was denied. As described above, Japanese and foreign clinical studies showed no relationship between ustekinumab and exacerbation or new onset of psoriasis and although the mechanism of exacerbation or new onset of psoriasis induced by anti-TNF agents has not been elucidated at molecular level, the molecular target of ustekinumab is different from that of anti-TNF agents. Therefore, this risk may be lower with ustekinumab compared with anti-TNF agents and a precautionary statement in the package insert etc. should be unnecessary at present.

PMDA accepts the applicant's response at present, but considers that it is necessary to collect further information on the effects of ustekinumab in patients with other diseases, etc. and continue to investigate the risk associated with ustekinumab because the clinical studies of ustekinumab were conducted primarily in psoriasis patients and it is difficult to appropriately assess exacerbation or new onset of psoriasis in psoriasis patients.

4.(ii).B.(4).2).(f) Injection site reactions and allergic reactions
In Japanese Study JPN-02, the incidences of injection site reactions were 0.6% (1 of 158 subjects) following administration of placebo and 1.9% (3 of 154 subjects) following administration of

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ustekinumab and these events were all mild in severity. While no cases of anaphylactic reactions or serum sickness reactions were reported, as adverse events of suspected allergic reactions, eczema (7.1% [11 of 154 subjects]), urticaria (3.9% [6 of 154 subjects]), pruritus (1.9% [3 of 154 subjects]), injection site urticaria (0.6% [1 of 154 subjects]), rash (0.6% [1 of 154 subjects]), and pruritus generalised (0.6% [1 of 154 subjects]) were observed. The incidence of anti-ustekinumab antibody development in the combined ustekinumab group was 6.5% and none of the antibody-positive subjects had an adverse event of suspected anaphylactic reaction and the 3 subjects with injection site reactions were not antibody-positive.

In pooled 3 foreign psoriasis studies, the incidences of injection site reactions were 2.6% (60 of 2304 subjects) following administration of placebo and 3.1% (71 of 2266 subjects) following administration of ustekinumab and no major differences were observed. Although no adverse events of suspected anaphylactic reactions or serum sickness-like reactions were observed, as adverse events of suspected allergic reactions, rash and urticaria were reported and the incidence was <1% for both events. The incidence of anti-ustekinumab antibody development in the combined ustekinumab group was 3.7% and none of the antibody-positive subjects had an adverse event of suspected anaphylactic reaction. In foreign phase III studies (Studies T08 and T09), the incidences of injection site reactions were 7.0% (5 of 71 subjects) in antibody-positive subjects and 3.8% (71 of 1870 subjects) in antibody-negative subjects, which indicated that there is no relationship between anti-ustekinumab antibody development and injection site reactions.

Based on the latest foreign post-marketing safety data, 1 case of anaphylactic reaction and 4 cases of hypersensitivity were collected and as it was considered that serious allergic reactions should be recognized as a risk associated with ustekinumab, it will be stated, as precaution information, in the adverse reactions section of the package insert that serious allergic reactions such as possible anaphylactic events and angioedema may occur.

PMDA considers as follows:
The precaution information concerning serious allergic reactions associated with ustekinumab is appropriate at present. Meanwhile, as it seems that the occurrence of serious allergic reactions tends to increase in the foreign post-marketing experience compared to in the clinical studies, it is necessary to continue to watch the trend of occurrence and review the precaution information as appropriate. During treatment with ustekinumab, it is important to be prepared so that drug therapy and emergency measures can be used promptly in response to anaphylaxis etc. and then to closely monitor the patient’s condition.

In addition, the occurrence of autoimmune disease, demyelinating disease, interstitial pneumonia, blood disorder, and hepatic disorder etc., which are considered to be important adverse reactions to anti-TNF agents (similar drugs), was also investigated based on the clinical study data and the latest foreign post-marketing safety data etc., which has suggested no risk of these adverse events associated

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with ustekinumab at present. Thus, no particular precaution information etc. are necessary. However, given that the clinical experience with ustekinumab is very limited compared to the experience with anti-TNF agents, that the mechanism of these adverse events associated with anti-TNF agents is not elucidated, and that anti-TNF agents and ustekinumab are both antibody products affecting the immune system, etc., the possibility that ustekinumab also causes similar adverse reactions cannot be denied. Therefore, it is necessary to carefully investigate the occurrence of these events also via post-marketing surveillance.

4.(ii).B.(5) Post-marketing safety measures

PMDA considers as follows:

Since the possibility that ustekinumab causes adverse reactions such as serious infections and malignancy cannot be denied and the long-term safety of ustekinumab is unknown in many aspects, as in the case of existing biologics, a large-scale drug use-results survey with the physicians and all the patients registered and a long-term special drug use-results survey to appropriately follow the patients for the development of malignancy, etc., should be conducted. In order to promote proper use of ustekinumab, information should be provided to healthcare providers and patients appropriately and promptly by giving detailed materials to healthcare providers such as physicians, developing a patient's guide etc., which describe the risks and benefits of ustekinumab in an appropriate and easy-to-understand manner, and collecting and disclosing post-marketing information accordingly via the Internet, etc.

Furthermore, dermatologists are the main physicians to treat psoriasis, and it is essential for them, prior to the use of ustekinumab, to establish cooperation with internists, etc., who are capable of handling serious adverse drug reactions such as infections, in terms of safety measures. Thus, PMDA asked the applicant to explain in details about the requirements for medical institutions to use ustekinumab and the specific way of cooperation with internists, etc.

The applicant explained as follows:

The requirements for medical institutions to use ustekinumab are as follows: Ustekinumab can be used under the management/supervision/guidance of specialist(s) who are familiar with the diagnosis and treatment of psoriasis and who know the risks of ustekinumab very well; and tuberculosis screening can be performed and adverse drug reactions including serious infections can be diagnosed and treated at the medical institution or in its affiliated medical institution. The requirements for affiliated medical institutions are as follows: tuberculosis screening can be performed and adverse drug reactions including serious infections can be diagnosed and treated in cooperation with the prescribing medical institution (except for general hospitals having relevant cooperating departments). Moreover, the procedures for cooperation between the medical institutions have been planned as follows: (a) Affiliated medical institutions and cooperating physicians there will be identified through contacts with physicians using ustekinumab and not only prescribing physicians but also cooperating physicians will be explained about the safety profile of ustekinumab and actions to be taken in the

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event of adverse drug reactions and the importance of determining whether or not to use ustekinumab, etc., (b) prescribing physicians will be requested to instruct their patients to contact them promptly if any abnormality occurs after administration of ustekinumab and to refer their patients to the affiliated medical institutions promptly if adverse drug reactions such as infections are suspected, and (c) portable patient cards for the patients to visit the affiliated medical institutions with and forms (patient diaries, etc.) that can be shared between the prescribing physicians and the affiliated medical institutions and that are used by patients themselves to record their health status will be prepared, etc.

As cooperation from the relevant academic societies, etc., is also considered essential for promoting proper use of ustekinumab and implementing safety measures, the Japanese Dermatological Association will be requested to take the initiative in developing a guideline for the use of ustekinumab.

PMDA considers as follows:
The applicant's response is largely acceptable, but it is important to confirm that cooperation with other departments/other medical institutions is ensured, via post-marketing surveillance.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the documents appended to the new drug application (5.3.3.2.1, 5.3.5.1.2-1). As a result, enrollment of subjects who met the exclusion criteria of the protocol and flaws in the contract for the partial transfer of trial-related duties were found at some trial sites, but PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of ustekinumab in the treatment of psoriasis vulgaris and psoriatic arthritis in patients who have had an inadequate response to conventional therapy has been demonstrated and its safety is acceptable in view of its observed benefits. Since ustekinumab is a

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biologic with a novel mechanism of action and offers a new therapeutic option, it has clinical significance. The INDICATION statement and the DOSAGE AND ADMINISTRATION statement need to be further discussed. Regarding safety, serious adverse drug reactions such as infections may occur following administration of ustekinumab. Therefore, prior to the use of ustekinumab, the patient's symptoms, etc. should be monitored closely and the risks and benefits of ustekinumab should be weighed. A post-marketing drug use-results survey, which covers all the patients treated with ustekinumab, should be conducted to further investigate the safety of ustekinumab in psoriasis patients.

The application may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

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Review Report (2)

November 10, 2010

I. Product Submitted for Registration

[Brand name] Stelara Subcutaneous Injection 45 mg Syringe
[Non-proprietary name] Ustekinumab (Genetical Recombination)
[Name of applicant] Janssen Pharmaceutical K.K.
[Date of application] January 21, 2010

II. Content of the Review

The outlines of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Indications

PMDA concluded that ustekinumab should be indicated only for the patients who have had an inadequate response or intolerance to phototherapy or conventional systemic therapy, which was supported by the expert advisors. PMDA considered that the INDICATION statement should be modified to include the following statements in the Precautions for Indications section of the package insert: ustekinumab should be used in (a) patients who have a body surface area involvement of ≥10% and who have had an inadequate response to conventional systemic therapy including UV-light therapy (excluding biologics) or (b) patients with refractory skin lesion or joint inflammation. PMDA requested the applicant to modify the indications and the applicant accepted it.

[Indications]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris and psoriatic arthritis

In addition, PMDA instructed the applicant to include in the package the statement to the effect that ustekinumab should only be used by physicians who are familiar with the treatment of psoriasis, etc. to ensure correct diagnosis, selection of eligible patients, and the proper use of ustekinumab, and that ustekinumab should be used in cooperation with internists, etc., who are capable of handling adverse reactions to ustekinumab. The applicant responded that in order to give adequate warning, it will be stated in the WARNING section of the package insert that ustekinumab should be used by physicians

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with experience in treating psoriasis in cooperation with physicians with adequate knowledge about ustekinumab.

(2) Dosage and administration

PMDA has concluded that a dose increase should be recommended as follows: "If the effect is insufficient, a dose of 90 mg may be used", which was supported by the expert advisors. PMDA considered that the DOSAGE AND ADMINISTRATION statement should be modified as shown below and that it should be stated in the Precautions of Dosage and Administration section that treatment with ustekinumab should not be continued without careful consideration if the patient does not respond to an increased dose of ustekinumab. PMDA requested the applicant to take actions accordingly and the applicant accepted it.

[Dosage and administration]
The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter.
If the effect is insufficient, a dose of 90 mg may be used.

Since ustekinumab is administered every 12 weeks after Week 4, it is not a heavy burden for most patients to receive injections at the medical institution. Therefore, patient self-administration has not been proposed.

(3) Post-marketing surveillance etc.

PMDA has concluded as follows

Ustekinumab may cause adverse reactions including serious infections. When ustekinumab is indicated for treatment of psoriasis, it is necessary to ensure the patient's safety with close cooperation between dermatologists and internists etc. Thus, after the market launch, a drug use-results survey, which covers all the patients treated with ustekinumab, should be conducted until data from a certain number of patient will be accumulated, in order to obtain safety information on ustekinumab in psoriasis patients as soon as possible and confirm the effectiveness of safety measures taken in cooperation with other departments/other medical institutions. Furthermore, a long-term, specified drug use-results survey to monitor the development of infections and malignancy should be conducted. On the basis of the above conclusion, PMDA requested the applicant to take actions accordingly.

The applicant responded as follows:

A long-term, specified drug use-results survey with an observation period of 52 weeks, which covers all the patients treated with ustekinumab, will be conducted. For this survey, (a) the priority items will be allergy, cardiac disorder, autoimmune disease, pancytopenia, interstitial pneumonia, demyelinating disease, and hepatic disorder, etc., which have been reported with anti-TNF agents, as well as infections, tuberculosis, and malignancy, (b) the following information will be collected: the efficacy and safety of an increased dose of ustekinumab, the safety of switching from other biologics to

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ustekinumab, the actual state of concomitant use with phototherapy or other systemic therapies, the effects of ustekinumab on atopic diseases such as asthma and the cardiovascular system, etc., the efficacy of ustekinumab in patients with diabetes co-morbidity, and disease activity as measured by DAS 28 in patients with psoriatic arthritis, etc. and (c) analyses will be performed when the information from 1500 patients have been collected, but the survey will be continued until the regulatory authority's final evaluation is obtained. Patients will be followed for the development of serious infections and malignancy for up to 3 years.

PMDA considers that the survey should be conducted promptly and the obtained results should be provided to clinical practice appropriately.

III. Overall Evaluation

As a result of the above review, PMDA concludes that ustekinumab may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indications]
Treatment of the following diseases in patients who have had an inadequate response to conventional therapy:
Psoriasis vulgaris and psoriatic arthritis

[Dosage and administration]
The usual initial adult dosage is 45 mg of Ustekinumab (Genetical Recombination) is administered subcutaneously, followed 4 weeks later by a 45 mg dose, and then every 12 weeks thereafter.
If the effect is insufficient, a dose of 90 mg may be used.

[Conditions for approval]
The applicant is required to:
(1) Conduct a post-marketing drug use-results survey, which covers all the patients treated with the product, until data from a certain number of patients will be accumulated, in order to collect data on the safety and efficacy of the product as soon as possible and to take necessary measures to ensure proper use of Ustekinumab.
(2) Conduct a large-scale post-marketing surveillance study to fully evaluate the safety of the product and to investigate the long-term safety of the product and the occurrence of infections etc.

https://web.archive.org/web/20190827202128/https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-stelara-ii/0071_en.pdf

25 July 2019
EMA/CHMP/408535/2019
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (post authorisation)

Stelara

ustekinumab

On 25 July 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Stelara. The marketing authorisation holder for this medicinal product is Janssen-Cilag International NV.

The CHMP adopted a new indication as follows:

> "Stelara is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1)."

For information, the full indications for Stelara will be as follows:

> "Plaque psoriasis
>
> Stelara is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).
>
> Paediatric plaque psoriasis
>
> Stelara is indicated for the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).
>
> Psoriatic arthritis (PsA)
>
> Stelara, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

[1] Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion

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Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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Crohn's Disease

Stelara is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative colitis

Stelara is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1)."

Detailed recommendations for the use of this product will be described in the updated summary of product characteristics (SmPC), which will be published in the revised European public assessment report (EPAR), and will be available in all official European Union languages after a decision on this change to the marketing authorisation has been granted by the European Commission.

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https://web.archive.org/web/20180814233654/http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STELARA® safely and effectively. See full prescribing information for STELARA®.

STELARA® (ustekinumab) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2009

---------- RECENT MAJOR CHANGES ----------

Indications and Usage, Psoriasis (1.1)	10/2017
Dosage and Administration (2.1)	10/2017
Dosage and Administration (2.4)	10/2017
Warnings and Precautions (5.9)	06/2018

---------- INDICATIONS AND USAGE ----------

STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of:

Adult patients with:

- *moderate to severe plaque psoriasis (Ps)* who are candidates for phototherapy or systemic therapy. (1.1)
- *active psoriatic arthritis (PsA)*, alone or in combination with methotrexate. (1.2)
- *moderately to severely active Crohn's disease (CD)* who have
  - failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker or
  - failed or were intolerant to treatment with one or more TNF blockers. (1.3)

Adolescent patients (12 years or older) with:

- *moderate to severe plaque psoriasis*, who are candidates for phototherapy or systemic therapy. (1.1)

---------- DOSAGE AND ADMINISTRATION ----------

Psoriasis Adult Subcutaneous Recommended Dosage (2.1):

Weight Range (kilogram)	Dosage Regimen
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks

Psoriasis Adolescent (12 years and older) Subcutaneous Recommended Dosage (2.1):

Weight based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilogram)	Dosage Regimen
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
greater than 100 kg	90 mg

Psoriatic Arthritis Adult Subcutaneous Recommended Dosage (2.2):

- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Crohn's Disease Initial Adult Intravenous Recommended Dosage (2.3):

A single intravenous infusion using weight-based dosing:

Weight Range (kilogram)	Recommended Dosage
up to 55 kg	260 mg (2 vials)
greater than 55 kg to 85 kg	390 mg (3 vials)
greater than 85 kg	520 mg (4 vials)

Crohn's Disease Maintenance Adult Subcutaneous Recommended Dosage (2.3):

A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

---------- DOSAGE FORMS AND STRENGTHS ----------

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL in a single-dose prefilled syringe (3)
- Injection: 45 mg/0.5 mL in a single-dose vial (3)

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial (3)

---------- CONTRAINDICATIONS ----------

Clinically significant hypersensitivity to ustekinumab or to any of the excipients. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing STELARA® until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STELARA®. Initiate treatment of latent TB before administering STELARA®. (5.3)
- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur. (5.5)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA®. (5.6)
- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment. (5.9)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions are:

- Psoriasis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)
- Crohn's Disease, induction (≥3%): vomiting. (6.1)
- Crohn's Disease, maintenance (≥3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2018

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STELARA® (ustekinumab)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Psoriasis (Ps)

STELARA® is indicated for the treatment of patients 12 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

STELARA® is indicated for the treatment of adult patients with active psoriatic arthritis. STELARA® can be used alone or in combination with methotrexate (MTX).

1.3 Crohn's Disease (CD)

STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have:

- failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker or
- failed or were intolerant to treatment with one or more TNF blockers.

2 DOSAGE AND ADMINISTRATION

2.1 Psoriasis

Subcutaneous Adult Dosage Regimen

- For patients weighing 100 kg or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

In subjects weighing more than 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects *[see Clinical Studies (14)]*.

Subcutaneous Adolescent Dosage Regimen

Administer STELARA® subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.

The recommended dose of STELARA® for adolescents (12-17 years old) based on body weight is shown below (Table 1).

Table 1: Recommended Dose of STELARA® for Subcutaneous Injection in Adolescent Patients with Psoriasis

Body Weight of Patient at the Time of Dosing	Recommended Dose
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
more than 100 kg	90 mg

For adolescent patients weighing less than 60 kg, the administration volume for the recommended dose (0.75 mg/kg) is shown in Table 2; withdraw the appropriate volume from the single-dose vial.

Table 2: Injection volumes of STELARA® 45 mg/0.5mL single-dose vials for adolescent psoriasis patients less than 60 kg

Body Weight (kg) at the time of dosing	Dose (mg)	Volume of injection (mL)
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

2.2 Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

2.3 Crohn's Disease

Intravenous Induction Adult Dosage Regimen

A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 3 *[see Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)]*.

Table 3: Initial Intravenous Dosage of STELARA®

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4

Subcutaneous Maintenance Adult Dosage Regimen

The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

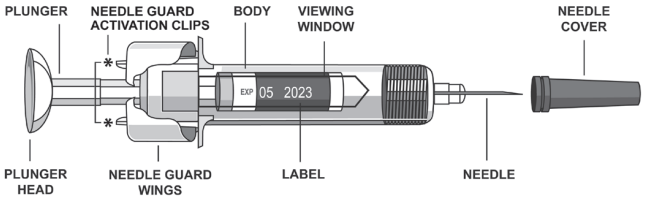
2.4 General Considerations for Administration

- STELARA® is intended for use under the guidance and supervision of a physician. STELARA® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. The appropriate dose should be determined by a healthcare provider using the patient's current weight at the time of dosing. In adolescent patients, it is recommended that STELARA® be administered by a health care provider. If a physician determines that it is appropriate, a patient may self-inject or a caregiver may inject STELARA® after proper training in subcutaneous injection technique. Patients should be instructed to follow the directions provided in the Medication Guide *[see Medication Guide]*.
- The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The needle cover should not be handled by persons sensitive to latex.
- It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated. When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch needle is recommended.
- Prior to administration, visually inspect STELARA® for particulate matter and discoloration. STELARA® is a colorless to light yellow solution and may contain a few small translucent or white particles. Do not use STELARA® if it is discolored or cloudy, or if other particulate matter is present. STELARA® does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

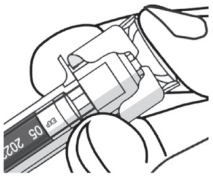
2.5 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard

Refer to the diagram below for the provided instructions.

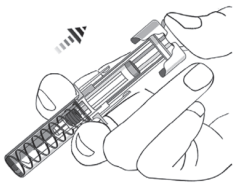
To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.



- Hold the BODY and remove the NEEDLE COVER. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE COVER or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE COVER in place.**
- Inject STELARA® subcutaneously as recommended *[see Dosage and Administration (2.1, 2.2, 2.3)]*.
- Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the needle guard wings. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard.**



- After injection, maintain the pressure on the PLUNGER HEAD and remove the needle from the skin. Slowly take your thumb off the PLUNGER HEAD to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by the illustration below:



- Used syringes should be placed in a puncture-resistant container.

2.6 Preparation and Administration of STELARA® 130 mg/26 mL (5 mg/mL) Vial for Intravenous Infusion (Crohn's Disease)

STELARA® solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA® vials needed based on patient weight (Table 3). Each 26 mL vial of STELARA® contains 130 mg of ustekinumab.
2. Withdraw, and then discard a volume of the 0.9% Sodium Chloride Injection, USP from the 250 mL infusion bag equal to the volume of STELARA® to be added (discard 26 mL sodium chloride for each vial of STELARA® needed, for 2 vials- discard 52 mL, for 3 vials- discard 78 mL, 4 vials- discard 104 mL).
3. Withdraw 26 mL of STELARA® from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion solution may be stored for up to four hours prior to infusion.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Do not infuse STELARA® concomitantly in the same intravenous line with other agents.
8. STELARA® does not contain preservatives. Each vial is for single use only. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be stored for up to 4 hours at room temperature up to 25°C (77°F). Do not freeze. Discard any unused portion of the infusion solution.

3 DOSAGE FORMS AND STRENGTHS

STELARA® (ustekinumab) is a colorless to light yellow solution and may contain a few small translucent or white particles.

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL solution in a single-dose vial

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

STELARA® is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

STELARA® may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in subjects receiving STELARA® *[see Adverse Reactions (6.1)]*.

Serious infections requiring hospitalization occurred in patients with psoriasis, psoriatic arthritis and Crohn's disease in clinical studies. In patients with psoriasis, serious infections included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections. In patients with psoriatic arthritis, serious infections included cholecystitis. In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, ophthalmic herpes, pneumonia, and listeria meningitis.

Treatment with STELARA® should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STELARA® in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with STELARA® and consider discontinuing STELARA® for serious or clinically significant infections until the infection resolves or is adequately treated.

5.2 Theoretical Risk for Vulnerability to Particular Infections

Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances.

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis infection prior to initiating treatment with STELARA®.

Do not administer STELARA® to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering STELARA®. Consider anti-tuberculosis therapy prior to initiation of STELARA® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving STELARA® for signs and symptoms of active tuberculosis during and after treatment.

5.4 Malignancies

STELARA® is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA® in clinical studies *[see Adverse Reactions (6.1)]*. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy *[see Nonclinical Toxicology (13)]*.

The safety of STELARA® has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

There have been post-marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving STELARA® who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving STELARA® should be monitored for the appearance of non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely *[see Adverse Reactions (6.1)]*.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with STELARA® *[see Adverse Reactions (6.1, 6.3)]*. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®.

5.6 Reversible Posterior Leukoencephalopathy Syndrome

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed in clinical studies of psoriasis and psoriatic arthritis. The subject, who had received 12 doses of STELARA® over approximately two years, presented with headache, seizures and confusion. No additional STELARA® injections were administered and the subject fully recovered with appropriate treatment. No cases of RPLS were observed in clinical studies of Crohn's disease.

RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported.

If RPLS is suspected, administer appropriate treatment and discontinue STELARA®.

5.7 Immunizations

Prior to initiating therapy with STELARA®, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with STELARA® should not receive live vaccines. BCG vaccines should not be given during treatment with STELARA® or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving STELARA® because of the potential risk for shedding from the household contact and transmission to patient.

Non-live vaccinations received during a course of STELARA® may not elicit an immune response sufficient to prevent disease.

5.8 Concomitant Therapies

In clinical studies of psoriasis the safety of STELARA® in combination with other immunosuppressive agents or phototherapy was not evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone *[see Nonclinical Toxicology (13.1)]*.

5.9 Noninfectious Pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment *[see Postmarketing Experience (6.3)]*.

STELARA® (ustekinumab)

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Subjects with Plaque Psoriasis

The safety data reflect exposure to STELARA® in 3117 adult psoriasis subjects, including 2414 exposed for at least 6 months, 1855 exposed for at least one year, 1653 exposed for at least two years, 1569 exposed for at least three years, 1482 exposed for at least four years and 838 exposed for at least five years.

Table 4 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the STELARA® groups than the placebo group during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14)]*.

Table 4: Adverse Reactions Reported by ≥1% of Subjects through Week 12 in Ps STUDY 1 and Ps STUDY 2

		STELARA®	
	Placebo	**45 mg**	**90 mg**
Subjects treated	**665**	**664**	**666**
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

Adverse reactions that occurred at rates less than 1% in the controlled period of Ps STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

One case of RPLS occurred during clinical studies *[see Warnings and Precautions (5.6)]*.

Infections

In the placebo-controlled period of clinical studies of psoriasis subjects (average follow-up of 12.6 weeks for placebo-treated subjects and 13.4 weeks for STELARA®-treated subjects), 27% of STELARA®-treated subjects reported infections (1.39 per subject-year of follow-up) compared with 24% of placebo-treated subjects (1.21 per subject-year of follow-up). Serious infections occurred in 0.3% of STELARA®-treated subjects (0.01 per subject-year of follow-up) and in 0.4% of placebo-treated subjects (0.02 per subject-year of follow-up) *[see Warnings and Precautions (5.1)]*.

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years), representing 8998 subject-years of exposure, 72.3% of STELARA®-treated subjects reported infections (0.87 per subject-years of follow-up). Serious infections were reported in 2.8% of subjects (0.01 per subject-years of follow-up).

Malignancies

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years, representing 8998 subject-years of exposure), 1.7% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of STELARA®-treated subjects (0.52 per hundred subject-years of follow-up) *[see Warnings and Precautions (5.4)]*. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical studies were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in STELARA®-treated patients during the controlled and uncontrolled portions of studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender and race).[1]

Adolescent Subjects with Plaque Psoriasis

The safety of STELARA® was assessed in a study of 110 subjects 12 to 17 years of age with moderate to severe plaque psoriasis. The safety profile in these subjects through Week 60 was similar to the safety profile from studies in adults with plaque psoriasis.

Psoriatic Arthritis

The safety of STELARA® was assessed in 927 patients in two randomized, double-blind, placebo-controlled studies in adult patients with active psoriatic arthritis (PsA). The overall safety profile of STELARA® in patients with PsA was consistent with the safety profile seen in adult psoriasis clinical studies. A higher incidence of arthralgia, nausea, and dental infections was observed in STELARA®-treated patients when compared with placebo-treated patients (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo-controlled portions of the PsA clinical studies.

Crohn's Disease

The safety of STELARA® was assessed in 1407 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter studies. These 1407 patients included 40 patients who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In Studies CD-1 and CD-2 there were 470 patients who received STELARA® 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3)]*. Patients who were responders in either Study CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or placebo for 44 weeks in Study CD-3. Patients in these 3 studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX)], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's disease *[see Clinical Studies (14.4)]*.

The overall safety profile of STELARA® was consistent with the safety profile seen in the adult psoriasis and psoriatic arthritis clinical studies. Common adverse reactions in Studies CD-1 and CD-2 and in Study CD-3 are listed in Tables 5 and 6, respectively.

Table 5: Common adverse reactions through Week 8 in Studies CD-1 and CD-2 occurring in ≥3% of STELARA®-treated patients and higher than placebo

	Placebo N=466	STELARA® 6 mg/kg single intravenous induction dose N=470
Vomiting	3%	4%

Other less common adverse reactions reported in patients in Studies CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 6: Common adverse reactions through Week 44 in Study CD-3 occurring in ≥3% of STELARA®-treated patients and higher than placebo

	Placebo N=133	STELARA® 90 mg subcutaneous maintenance dose every 8 weeks N=131
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

Infections

In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes were reported in one patient each.

Malignancies

With up to one year of treatment in the Crohn's disease clinical studies, 0.2% of STELARA®-treated patients (0.36 events per hundred patient-years) and 0.2% of placebo-treated patients (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.2% of STELARA®-treated patients (0.27 events per hundred patient-years) and in none of the placebo-treated patients.

Hypersensitivity Reactions Including Anaphylaxis

In CD studies, two patients reported hypersensitivity reactions following STELARA® administration. One patient experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of patients receiving subcutaneous STELARA®). In addition, one patient experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous STELARA® dose (0.08% of patients receiving intravenous STELARA®). These patients were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour.

STELARA® (ustekinumab)

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ustekinumab in the studies described below with the incidence of antibodies to other products may be misleading.

Approximately 6-12.4% of subjects treated with STELARA® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titer. In Crohn's disease clinical studies, less than 3% of patients treated with STELARA® developed antibodies to ustekinumab. In psoriasis clinical studies, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen. In psoriasis studies, the majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval of STELARA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to STELARA® exposure.

Immune system disorders: Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria) *[see Warnings and Precautions (5.5)]*.

Respiratory, thoracic and mediastinal disorders: Interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia *[see Warnings and Precautions (5.9)]*.

Skin reactions: Pustular psoriasis, erythrodermic psoriasis.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines with STELARA® *[see Warnings and Precautions (5.7)]*.

7.2 Concomitant Therapies

In psoriasis studies the safety of STELARA® in combination with immunosuppressive agents or phototherapy has not been evaluated *[see Warnings and Precautions (5.8)]*. In psoriatic arthritis studies, concomitant methotrexate use did not appear to influence the safety or efficacy of STELARA®. In Crohn's disease studies, immunomodulators (6-mercaptopurine, azathioprine, methotrexate) were used concomitantly in approximately 30% of patients and corticosteroids were used concomitantly in approximately 40% of patients. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of STELARA®.

7.3 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, STELARA®, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA® in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed *[see Clinical Pharmacology (12.3)]*.

7.4 Allergen Immunotherapy

STELARA® has not been evaluated in patients who have undergone allergy immunotherapy. STELARA® may decrease the protective effect of allergen immunotherapy (decrease tolerance) which may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergen immunotherapy, particularly for anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to STELARA® during pregnancy. Patients should be encouraged to enroll by calling 1-877-311-8972.

Risk Summary

Limited data on the use of STELARA® in pregnant women are insufficient to inform a drug associated risk *[see Data]*. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the human exposure at the maximum recommended human subcutaneous dose (MRHD).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Limited data on use of STELARA® in pregnant women from observational studies, published case reports, and postmarketing surveillance are insufficient to inform a drug associated risk.

Animal Data

Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks.

In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly at exposures greater than 100 times the human subcutaneous exposure from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab-related effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of ustekinumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ustekinumab was present in the milk of lactating monkeys administered ustekinumab. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Maternal IgG is known to be present in human milk. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule and is degraded in the gastrointestinal tract. However, if ustekinumab is transferred into human milk the effects of local exposure in the gastrointestinal tract are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STELARA® and any potential adverse effects on the breastfed child from STELARA® or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of STELARA® have been established in pediatric subjects 12 to 17 years old with moderate to severe plaque psoriasis. Use of STELARA® in this age group is supported by evidence from a multicenter, randomized, 60-week trial that included a 12-week, double-blind, placebo-controlled, parallel-group portion, in 110 pediatric subjects 12 years and older *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*. The safety and effectiveness of STELARA® for pediatric patients less than 12 years of age have not been established.

8.5 Geriatric Use

Of the 5884 subjects exposed to STELARA®, a total of 306 were 65 years or older (183 patients with psoriasis, 65 patients with psoriatic arthritis and 58 with Crohn's disease), and 34 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

Single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, ustekinumab is produced in a well characterized recombinant cell line and is purified using standard bio-processing technology. The manufacturing process contains steps for the clearance of viruses. Ustekinumab is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles with pH of 5.7- 6.3.

STELARA® for Subcutaneous Use

Available as 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL, supplied as a sterile solution in a single-dose prefilled syringe with a 27 gauge fixed ½ inch needle and as 45 mg of ustekinumab in 0.5 mL in a single-dose 2 mL Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cover that contains dry natural rubber (a derivative of latex).

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

STELARA® for Intravenous Infusion

Available as 130 mg of ustekinumab in 26 mL, supplied as a single-dose 30 mL Type I glass vial with a coated stopper.

STELARA® (ustekinumab)

Each 26 mL vial delivers 130 mg ustekinumab, EDTA disodium salt dihydrate (0.52 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's disease. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

12.2 Pharmacodynamics

In a small exploratory study, a decrease was observed in the expression of mRNA of its molecular targets IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to two weeks post-treatment in subjects with psoriasis.

12.3 Pharmacokinetics

Absorption

In adult subjects with psoriasis, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in subjects with psoriasis.

Following multiple subcutaneous doses of STELARA® in adult subjects with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean (±SD) steady-state trough serum ustekinumab concentrations were 0.69 ± 0.69 mcg/mL for patients less than or equal to 100 kg receiving a 45 mg dose and 0.74 ± 0.78 mcg/mL for patients greater than 100 kg receiving a 90 mg dose. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease, following the recommended intravenous induction dose, mean ±SD peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL. Starting at Week 8, the recommended subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in ustekinumab concentration over time when given subcutaneously every 8 weeks. Mean ±SD steady-state trough concentration was 2.51 ± 2.06 mcg/mL for 90 mg ustekinumab administered every 8 weeks.

Distribution

In a population pharmacokinetic analysis of ustekinumab, the volume of distribution of the central compartment was 2.74 L (95% CI: 2.69, 2.78), and the total volume of distribution at steady-state was 4.62 L in patients with Crohn's disease.

Elimination

The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following subcutaneous administration. In a population pharmacokinetic analysis of ustekinumab, the clearance was 0.19 L/day (95% CI: 0.185, 0.197) with an estimated median terminal half-life of approximately 19 days in patients with Crohn's disease.

Metabolism

The metabolic pathway of ustekinumab has not been characterized. As a human IgG1κ monoclonal antibody, ustekinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Specific Populations

Weight

When given the same dose, subjects with psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of higher weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group.

Age: Geriatric Population

A population pharmacokinetic analysis (N=106/1937 patients with psoriasis greater than or equal to 65 years old) was performed to evaluate the effect of age on the pharmacokinetics of ustekinumab. There were no apparent changes in pharmacokinetic parameters (clearance and volume of distribution) in subjects older than 65 years old.

Age: Pediatric Population

Following multiple recommended doses of STELARA® in adolescent subjects 12 to 17 years of age with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentration was 0.54 ± 0.43 mcg/mL.

Drug Interaction Studies

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). However, the clinical relevance of *in vitro* data has not been established *[see Drug Interactions (7.3)]*.

No *in vivo* drug interaction studies have been conducted with STELARA®.

Population pharmacokinetic data analyses indicated that the clearance of ustekinumab was not impacted by concomitant MTX, NSAIDs, and oral corticosteroids, or prior exposure to a TNF blocker in patients with psoriatic arthritis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of STELARA®. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, prior to and during early pregnancy.

13.2 Animal Toxicology and/or Pharmacology

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection.

14 CLINICAL STUDIES

14.1 Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled studies (Ps STUDY 1 and Ps STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies.

Ps STUDY 1 enrolled 766 subjects and Ps STUDY 2 enrolled 1230 subjects. The studies had the same design through Week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of STELARA®. Subjects randomized to STELARA® received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA® (either 45 mg or 90 mg) at Weeks 12 and 16.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

In both studies, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in Ps STUDY 1 and 40% of subjects in Ps STUDY 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of subjects had a history of psoriatic arthritis.

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 7 below.

Table 7: Clinical Outcomes Ps STUDY 1 and Ps STUDY 2

Week 12	Ps STUDY 1			Ps STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PGA of Cleared or Minimal	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)

Examination of age, gender, and race subgroups did not identify differences in response to STELARA® among these subgroups.

In subjects who weighed 100 kg or less, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 8 below).

Table 8: Clinical Outcomes by Weight Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			Ps STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response at Week 12*						
≤100 kg	4% 6/166	74% 124/168	65% 107/164	4% 12/290	73% 218/297	78% 225/289
>100 kg	2% 2/89	54% 47/87	68% 63/92	3% 3/120	49% 55/112	71% 86/121
PGA of Cleared or Minimal at Week 12*						
≤100 kg	4% 7/166	64% 108/168	63% 103/164	5% 14/290	74% 220/297	75% 216/289
>100 kg	3% 3/89	49% 43/87	58% 53/92	3% 4/120	51% 57/112	69% 84/121

* Patients were dosed with study medication at Weeks 0 and 4.

Subjects in Ps STUDY 1 who were PASI 75 responders at both Weeks 28 and 40 were re-randomized at Week 40 to either continued dosing of STELARA® (STELARA® at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to STELARA® treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks.

14.2 Adolescent Subjects with Plaque Psoriasis

A multicenter, randomized, double blind, placebo controlled study (Ps STUDY 3) enrolled 110 adolescent subjects 12 to 17 years of age with a minimum BSA involvement of 10%, a PASI score greater than or equal to 12, and a PGA score greater than or equal to 3, who were candidates for phototherapy or systemic therapy and whose disease was inadequately controlled by topical therapy.

Subjects were randomized to receive placebo (n = 37), the recommended dose of STELARA® (n = 36), or one-half the recommended dose of STELARA® (n = 37) by subcutaneous injection at Weeks 0 and 4 followed by dosing every 12 weeks (q12w). The recommended dose of STELARA® was 0.75 mg/kg for subjects weighing less than 60 kg, 45 mg for subjects weighing 60 kg to 100 kg, and 90 mg for subjects weighing greater than 100 kg. At Week 12, subjects who received placebo were crossed over to receive STELARA® at the recommended dose or one-half the recommended dose.

Of the adolescent subjects, approximately 63% had prior exposure to phototherapy or conventional systemic therapy and approximately 11% had prior exposure to biologics.

The endpoints were the proportion of patients who achieved a PGA score of cleared (0) or minimal (1), PASI 75, and PASI 90 at Week 12. Subjects were followed for up to 60 weeks following first administration of study agent.

Clinical Response

The efficacy results at Week 12 for Ps STUDY 3 are presented in Table 9.

Table 9: Summary of Efficacy Endpoints in the Adolescent Psoriasis Study at Week 12

	Ps STUDY 3	
	Placebo n (%)	STELARA®* n (%)
N	**37**	**36**
PGA		
PGA of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)
PASI		
PASI 75 responders	4 (10.8%)	29 (80.6%)
PASI 90 responders	2 (5.4%)	22 (61.1%)

* Using the weight-based dosage regimen specified in Table 1 and Table 2.

14.3 Psoriatic Arthritis

The safety and efficacy of STELARA® was assessed in 927 patients (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled studies in adult patients 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Patients were randomized to receive treatment with STELARA® 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)-α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the patients had been previously treated with TNF blocker, of whom over 70% had discontinued their TNF blocker treatment for lack of efficacy or intolerance at any time.

Clinical Response

In both studies, a greater proportion of patients achieved ACR 20, ACR 50 and PASI 75 response in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 10). ACR 70 responses were also higher in the STELARA® 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in STUDY 2. Responses were similar in patients regardless of prior TNFα exposure.

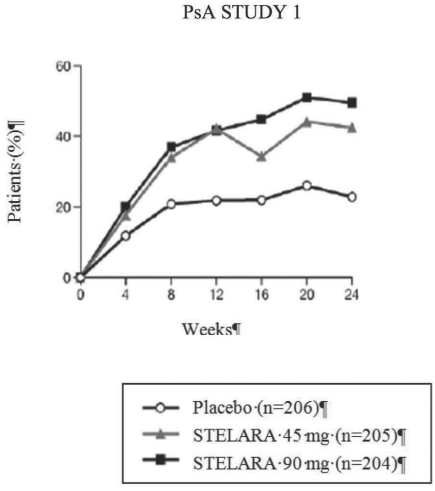
Table 10: ACR 20, ACR 50, ACR 70 and PASI 75 responses in PsA STUDY 1 and PsA STUDY 2 at Week 24

	PsA STUDY 1			PsA STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Number of patients randomized	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)	7 (7%)	18 (17%)	24 (23%)
ACR 70 response, N (%)	5 (2%)	25 (12%)	29 (14%)	3 (3%)	7 (7%)	9 (9%)
Number of patients with ≥ 3% BSA[a]	**146**	**145**	**149**	**80**	**80**	**81**
PASI 75 response, N (%)	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)

[a] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

The percent of patients achieving ACR 20 responses by visit is shown in Figure 1.

Figure 1: Percent of patients achieving ACR 20 response through Week 24



The results of the components of the ACR response criteria are shown in Table 11.

STELARA® (ustekinumab)

Table 11: Mean change from baseline in ACR components at Week 24

	PsA STUDY 1 STELARA®		
	Placebo (N=206)	45 mg (N= 205)	90 mg (N= 204)
Number of swollen joints[a]			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints[b]			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Patient's assessment of pain[c]			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Patient global assessment[c]			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment[c]			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ)[d]			
Baseline	1.2	1.2	1.2
Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)[e]			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

[a] Number of swollen joints counted (0-66)
[b] Number of tender joints counted (0-68)
[c] Visual analogue scale; 0= best, 10=worst.
[d] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.
[e] CRP: (Normal Range 0.0-1.0 mg/dL)

An improvement in enthesitis and dactylitis scores was observed in each STELARA® group compared with placebo at Week 24.

Physical Function

STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by HAQ-DI at Week 24. In both studies, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24.

14.4 Crohn's Disease

STELARA® was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy.

Studies CD-1 and CD-2

In studies CD-1 and CD-2, 1409 patients were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, patients were randomized to receive a single intravenous administration of STELARA® at either approximately 6 mg/kg, placebo (see Table 3), or 130 mg (a lower dose than recommended).

In Study CD-1, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 319 in the STELARA® approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator (6-mercaptopurine, azathioprine, methotrexate; 68% of patients), or both (49% of patients). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 286 in the STELARA® and 290 in the placebo group.

In these induction studies, a greater proportion of patients treated with STELARA®

achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 12 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in STELARA®-treated patients and continued to improve through Week 8.

Table 12: Induction of Clinical Response and Remission in CD-1* and CD-2**

	CD-1 n=741			CD-2 n=627		
	Placebo N=247	STELARA®† N=249	Treatment difference and 95% CI	Placebo N=209	STELARA®† N=209	Treatment difference and 95% CI
Clinical Response (100 point), Week 6	53 (21%)	84 (34%)[a]	12% (4%, 20%)	60 (29%)	116 (56%)[b]	27% (18%, 36%)
Clinical Remission, Week 8	18 (7%)	52 (21%)[b]	14% (8%, 20%)	41 (20%)	84 (40%)[b]	21% (12%, 29%)
Clinical Response (100 point), Week 8	50 (20%)	94 (38%)[b]	18% (10%, 25%)	67 (32%)	121 (58%)[b]	26% (17%, 35%)
70 Point Response, Week 6	75 (30%)	109 (44%)[a]	13% (5%, 22%)	81 (39%)	135 (65%)[b]	26% (17%, 35%)
70 Point Response, Week 3	67 (27%)	101 (41%)[a]	13% (5%, 22%)	66 (32%)	106 (51%)[b]	19% (10%, 28%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission: 70 point response is defined as reduction in CDAI score by at least 70 points

* Patient population consisted of patients who failed or were intolerant to TNF blocker therapy

** Patient population consisted of patients who failed or were intolerant to corticosteroids or immunomodulators (e.g., 6-mercaptopurine, azathioprine, methotrexate) and previously received but not failed a TNF blocker or were never treated with a TNF blocker.

† Infusion dose of STELARA® using the weight-based dosage regimen specified in Table 3.

[a] $0.001 \leq p < 0.01$

[b] $p < 0.001$

Study CD-3

The maintenance study (CD-3), evaluated 388 patients who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 of induction with STELARA® in studies CD-1 or CD-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks or placebo for 44 weeks (see Table 13).

Table 13: Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* N=131†	90 mg STELARA® every 8 weeks N=128†	Treatment difference and 95% CI
Clinical Remission	47 (36%)	68 (53%)[a]	17% (5%, 29%)
Clinical Response	58 (44%)	76 (59%)[b]	15% (3%, 27%)
Clinical Remission in patients in remission at the start of maintenance therapy**	36/79 (46%)	52/78 (67%)[a]	21% (6%, 36%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to STELARA® and were randomized to receive placebo at the start of maintenance therapy.

** Patients in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.

† Patients who achieved clinical response to STELARA® at the end of the induction study.

[a] $p < 0.01$

[b] $0.01 \leq p < 0.05$

At Week 44, 47% of patients who received STELARA® were corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group.

At Week 0 of Study CD-3, 34/56 (61%) STELARA® treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44.

At Week 0 of Study CD-3, 46/72 (64%) STELARA® treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of STELARA® treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

Patients who were not in clinical response 8 weeks after STELARA® induction were not included in the primary efficacy analyses for Study CD-3; however, these patients were eligible to receive a 90 mg subcutaneous injection of STELARA® upon entry into Study CD-3. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

15 REFERENCES

1 Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 6.6.2 Regs Research Data, Nov 2009 Sub (1973-2007) - Linked To County Attributes - Total U.S., 1969-2007 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2010, based on the November 2009 submission.

16 HOW SUPPLIED/STORAGE AND HANDLING

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials.

For Subcutaneous Use

Prefilled Syringes

- 45 mg/0.5 mL (NDC 57894-060-03)
- 90 mg/mL (NDC 57894-061-03)

Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber.

Single-dose Vial

- 45 mg/0.5 mL (NDC 57894-060-02)

For Intravenous Infusion

Single-dose Vial

- 130 mg/26 mL (5 mg/mL) (NDC 57894-054-27)

Storage and Stability

STELARA® vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store STELARA® vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) before the patient starts using STELARA®, and each time the prescription is renewed, as there may be new information they need to know.

Infections

Inform patients that STELARA® may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients of the risk of developing malignancies while receiving STELARA® *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

- Advise patients to seek immediate medical attention if they experience any signs or symptoms of serious hypersensitivity reactions and discontinue STELARA® *[see Warnings and Precautions (5.5)]*.
- Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex *[see Dosage and Administration (2.4)]*

Immunizations

Inform patients that STELARA® can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions (5.7)]*.

Pregnancy Registry

Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to STELARA® *[see Use in Specific Populations (8.1)]*.

Administration

Instruct patients to follow sharps disposal recommendations, as described in the Instructions for Use.

Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Cilag AG, Schaffhausen, Switzerland

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janssen

MEDICATION GUIDE
STELARA (stel ar' a)
(ustekinumab)
injection, for subcutaneous or intravenous use

What is the most important information I should know about STELARA?

STELARA is a medicine that affects your immune system. STELARA can increase your risk of having serious side effects, including:

Serious infections. STELARA may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections while taking STELARA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.

- Your doctor should check you for TB before starting STELARA.
- If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with STELARA and during treatment with STELARA.
- Your doctor should watch you closely for signs and symptoms of TB while you are being treated with STELARA.

You should not start taking STELARA if you have any kind of infection unless your doctor says it is okay.

Before starting STELARA, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have TB, or have been in close contact with someone with TB.

After starting STELARA, call your doctor right away if you have any symptoms of an infection (see above). STELARA can make you more likely to get infections or make an infection that you have worse. People who have a genetic problem where the body does not make any of the proteins interleukin 12 (IL-12) and interleukin 23 (IL-23) are at a higher risk for certain serious infections. These infections can spread throughout the body and cause death. People who take STELARA may also be more likely to get these infections.

Cancers. STELARA may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your doctor if you have ever had any type of cancer. Some people who are receiving STELARA and have risk factors for skin cancer have developed certain types of skin cancers. During your treatment with STELARA, tell your doctor if you develop any new skin growths.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). RPLS is a rare condition that affects the brain and can cause death. The cause of RPLS is not known. If RPLS is found early and treated, most people recover. Tell your doctor right away if you have any new or worsening medical problems including:

- headache
- seizures
- confusion
- vision problems

What is STELARA?

STELARA is a prescription medicine used to treat:

- adults and children 12 years and older with moderate or severe psoriasis who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).
- adults 18 years and older with active psoriatic arthritis. STELARA can be used alone or with the medicine methotrexate.
- adults 18 years and older with moderately to severely active Crohn's disease who have already taken other medicines that did not work well enough or they could not tolerate it.

It is not known if STELARA is safe and effective in children less than 12 years of age.

Do not take STELARA if you are allergic to ustekinumab or any of the ingredients in STELARA. See the end of this Medication Guide for a complete list of ingredients in STELARA.

Before you receive STELARA, tell your doctor about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section **"What is the most important information I should know about STELARA?"**
- ever had an allergic reaction to STELARA. Ask your doctor if you are not sure.
- are allergic to latex. The needle cover on the prefilled syringe contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who take STELARA should not receive live vaccines. Tell your doctor if anyone in your house needs a live vaccine. The viruses used in some types of live vaccines can spread to people with a weakened immune system, and can cause serious problems. **You should not receive the BCG vaccine during the one year before receiving STELARA or one year after you stop receiving STELARA.**
- have any new or changing lesions within psoriasis areas or on normal skin.
- are receiving or have received allergy shots, especially for serious allergic reactions. Allergy shots may not work as well for you during treatment with STELARA. STELARA may also increase your risk of having an allergic reaction to an allergy shot.
- receive or have received phototherapy for your psoriasis.
- are pregnant or planning to become pregnant. It is not known if STELARA can harm your unborn baby. You and your doctor should decide if you will receive STELARA. There is a pregnancy registry for women who are treated with STELARA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you are pregnant or become pregnant while receiving STELARA, talk to your doctor about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.
- are breastfeeding or plan to breastfeed. It is thought that STELARA passes into your breast milk in small amounts.
- Talk to your doctor about the best way to feed your baby if you receive STELARA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use STELARA?

- Use STELARA exactly as your doctor tells you to.
- **The needle cover on the STELARA prefilled syringe contains latex. Do not handle the needle cover if you are sensitive to latex.**
- Adults with Crohn's disease will receive the first dose of STELARA through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. It takes at least 1 hour to receive the full dose of medicine. You will then receive STELARA as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of STELARA, as described below.
- Adults with psoriasis or psoriatic arthritis and children 12 years and older with psoriasis will receive STELARA as an injection under the skin (subcutaneous injection) as described below.
- **Injecting STELARA under your skin**
  - STELARA is intended for use under the guidance and supervision of your doctor. In children 12 years and older, it is recommended that STELARA be administered by a healthcare provider. If your doctor decides that you or a caregiver may give your injections of STELARA at home, you should receive training on the right way to prepare and inject STELARA. Your doctor will determine the right dose of STELARA for you, the amount for each injection, and how often you should receive it. Do not try to inject STELARA yourself until you or your caregiver have been shown how to inject STELARA by your doctor or nurse.
  - Inject STELARA under the skin (subcutaneous injection) in your upper arms, buttocks, upper legs (thighs) or stomach area (abdomen).
  - Do not give an injection in an area of the skin that is tender, bruised, red or hard.
  - Use a different injection site each time you use STELARA.
  - If you inject more STELARA than prescribed, call your doctor right away.
  - Be sure to keep all of your scheduled follow-up appointments.

Read the detailed Instructions for Use at the end of this Medication Guide for instructions about how to prepare and inject a dose of STELARA, and how to properly throw away (dispose of) used needles and syringes. The syringe, needle and vial must never be re-used. After the cap is punctured, STELARA can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused portion of STELARA.

What should I avoid while using STELARA?

You should not receive a live vaccine while taking STELARA. See **"Before you receive STELARA, tell your doctor about all of your medical conditions, including if you:"**

What are the possible side effects of STELARA?

STELARA may cause serious side effects, including:

- See **"What is the most important information I should know about STELARA?"**
- **Serious allergic reactions.** Serious allergic reactions can occur with STELARA. Stop using STELARA and get medical help right away if you have any of the following symptoms of a serious allergic reaction:
  - feeling faint
  - swelling of your face, eyelids, tongue, or throat
  - chest tightness
  - skin rash
- **Lung inflammation.** Cases of lung inflammation have happened in some people who receive STELARA, and may be serious. These lung problems may need to be treated in a hospital. Tell your doctor right away if you develop shortness of breath or a cough that doesn't go away during treatment with STELARA.

Common side effects of STELARA include:

- upper respiratory infections
- headache
- tiredness
- itching
- vomiting
- vaginal yeast infections
- urinary tract infections
- redness at the injection site

These are not all of the possible side effects of STELARA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Janssen Biotech, Inc. at 1-800 JANSSEN (1-800-526-7736).

How should I store STELARA?

- Store STELARA prefilled syringes in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Store STELARA vials standing up straight.
- Store STELARA in the original carton to protect it from light until time to use it.
- Do not freeze STELARA.
- Do not shake STELARA.

Keep STELARA and all medicines out of the reach of children.

General information about the safe and effective use of STELARA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use STELARA for a condition for which it was not prescribed. Do not give STELARA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about STELARA that was written for health professionals.

What are the ingredients in STELARA?

Active ingredient: ustekinumab

Inactive ingredients: Single-dose prefilled syringe for subcutaneous use contains L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, and sucrose. **Single-dose vial for subcutaneous use** contains L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80 and sucrose. **Single-dose vial for intravenous infusion** contains EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, Polysorbate 80, and sucrose.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864

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For more information, go to *www.stelarainfo.com* or call 1-800-JANSSEN (1-800-526-7736).

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 06/2018

janssen

INSTRUCTIONS FOR USE
STELARA (stel ar' a**)**
(ustekinumab)
injection, for subcutaneous use

Instructions for injecting STELARA using a prefilled syringe.

Read this Instructions for Use before you start using STELARA. Your doctor or nurse should show you how to prepare and give your injection of STELARA the right way.

If you cannot give yourself the injection:

- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

Do not try to inject STELARA yourself until you have been shown how to inject STELARA by your doctor, nurse or health professional.

Important information:

- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
  - If your dose is 45 mg, you will receive one 45 mg prefilled syringe.
  - If your dose is 90 mg, you will receive either one 90 mg prefilled syringe or two 45 mg prefilled syringes. **If you receive two 45 mg prefilled syringes for a 90 mg dose, you will need to give yourself two injections, one right after the other.**
- Children 12 years of age and older with psoriasis who weigh 132 pounds or more may use a prefilled syringe.
- Check the expiration date on the prefilled syringe and carton. If the expiration date has passed, do not use it. If the expiration date has passed call your doctor or pharmacist, or call 1-800-JANSSEN (1-800-526-7736) for help.
- Make sure the syringe is not damaged.
- **The needle cover on the prefilled syringe contains latex. Do not handle the needle cover on the STELARA prefilled syringe if you are allergic to latex.**
- Check your prefilled syringe for any particles or discoloration. Your prefilled syringe should look clear and colorless to light yellow with few white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new prefilled syringe.
- **Do not shake the prefilled syringe at any time.** Shaking your prefilled syringe may damage your STELARA medicine. If your prefilled syringe has been shaken, do not use it. Get a new prefilled syringe.
- To reduce the risk of accidental needle sticks, each prefilled syringe has a needle guard that is automatically activated to cover the needle after you have given your injection. Do not pull back on the plunger at any time.

Gather the supplies you will need to prepare and to give your injection. (See Figure A)

You will need:

- antiseptic wipes
- cotton balls or gauze pads
- adhesive bandage
- your prescribed dose of STELARA **(See Figure B)**
- FDA-cleared sharps disposal container. **See "Step 4: Dispose of the syringe."**

Figure A

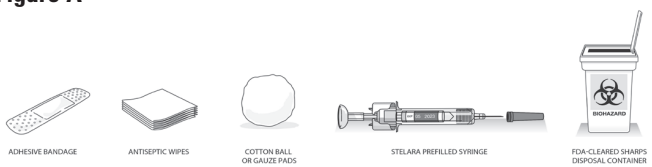
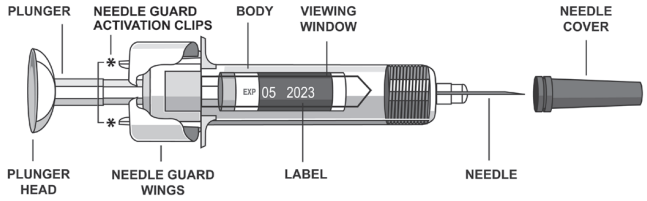


Figure B

To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.



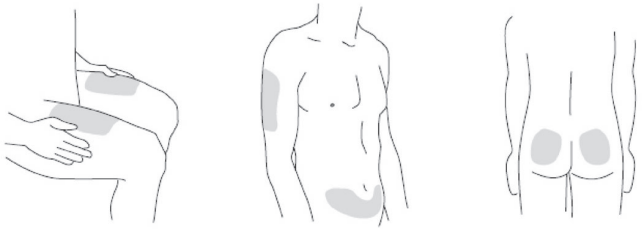
Step 1: Prepare the injection.

- Choose a well-lit, clean, flat work surface.
- Wash your hands well with soap and warm water.
- Hold the prefilled syringe with the covered needle pointing upward.

Step 2: Prepare your injection site

- Choose an injection site around your stomach area (abdomen), buttocks, upper legs (thighs). If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(See Figure C)**
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give your injection.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

Figure C

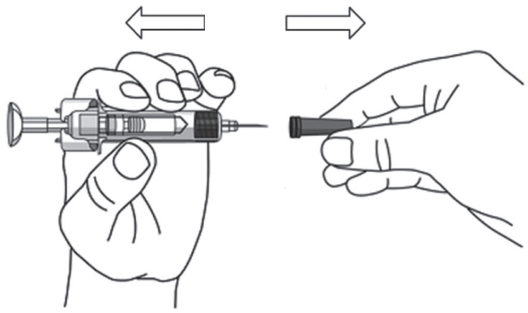


*Areas in gray are recommended injection sites.

Step 3: Inject STELARA

- Remove the needle cover when you are ready to inject your STELARA.
- **Do not** touch the plunger while removing the needle cover.
- Hold the body of the prefilled syringe with one hand, and pull the needle cover straight off. **(see Figure D)**
- Put the needle cover in the trash.
- You may also see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch the needle or let it touch anything.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place. Call your doctor, nurse or health professional for instructions.

Figure D



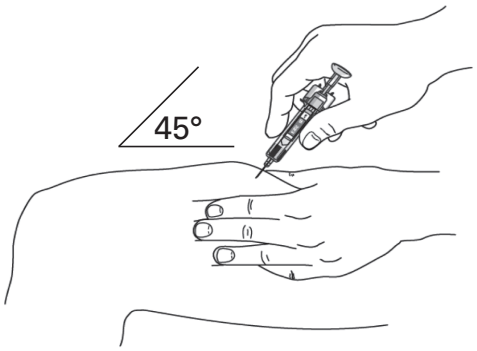
- Hold the body of the prefilled syringe in one hand between the thumb and index fingers. **(See Figure E)**

Figure E



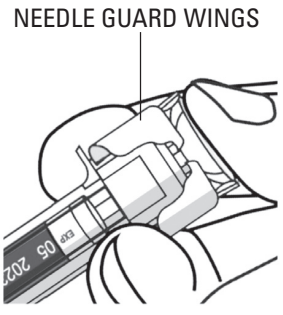
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure F)**

Figure F



- Inject all of the liquid by using your thumb to push in the plunger until the plunger head is completely between the needle guard wings. **(See Figure G)**

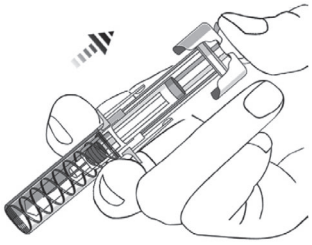
Figure G



STELARA® (ustekinumab)

- When the plunger is pushed as far as it will go, keep pressure on the plunger head. Take the needle out of the skin and let go of the skin.
- Slowly take your thumb off the plunger head. This will let the empty syringe move up until the entire needle is covered by the needle guard. **(See Figure H)**

Figure H



- When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

If your dose is 90 mg, you will receive either one 90 mg prefilled syringe or two 45 mg prefilled syringes. If you receive two 45 mg prefilled syringes for a 90 mg dose, you will need to give yourself a second injection right after the first. Repeat Steps 1-3 for the second injection using a new syringe. Choose a different site for the second injection.

Step 4: Dispose of the syringe.

- Put the syringe in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic.
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out.
  - upright and stable during use,
  - leak-resistant,
  - and properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your sharps disposal container.
- If you have any questions, talk to your doctor or pharmacist.

Keep STELARA and all medicines out of the reach of children.

Prefilled Syringe Manufactured by:
Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864
at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and
at Cilag AG, Schaffhausen, Switzerland

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 10/2017

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INSTRUCTIONS FOR USE
STELARA (stel ar' a**)**
(ustekinumab)
injection, for subcutaneous use

Instructions for injecting STELARA from a vial.

Read this Instructions for Use before you start using STELARA. Your doctor or nurse should show you how to prepare, measure your dose, and give your injection of STELARA the right way.

If you cannot give yourself the injection:
- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

Do not try to inject STELARA yourself until you have been shown how to inject STELARA by your doctor, nurse or health professional.

Important information:
- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
  - If your dose is 45 mg or less you will receive one 45 mg vial.
  - If your dose is 90 mg, you will receive two 45 mg vials **and you will need to give yourself two injections, one right after the other.**
- Children 12 years of age and older weighing less than 132 pounds require a dose lower than 45 mg.
- Check the expiration date on the vial and carton. If the expiration date has passed, do not use it. If the expiration date has passed, call your doctor or pharmacist, or call 1-800-JANSSEN (1-800-526-7736) for help.
- Check the vial for any particles or discoloration. Your vial should look clear and colorless to light yellow with few white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new vial.
- **Do not shake the vial at any time.** Shaking your vial may damage your STELARA medicine. If your vial has been shaken, do not use it. Get a new vial.
- Do not use a STELARA vial more than one time, even if there is medicine left in the vial. After the cap is punctured, STELARA can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused STELARA after you give your injection.
- Safely throw away (dispose of) STELARA vials after use.
- Do not re-use syringes or needles. See "**Step 6: Dispose of needles and syringes.**"
- To avoid needle-stick injuries, **do not** recap needles.

Gather the supplies you will need to prepare STELARA and to give your injection. (See Figure A)
You will need:
- a syringe with the needle attached, provided by your pharmacy
- antiseptic wipes
- cotton balls or gauze pads
- adhesive bandage
- your prescribed dose of STELARA
- FDA-cleared sharps disposal container. See "**Step 6: Dispose of needles and syringes.**"

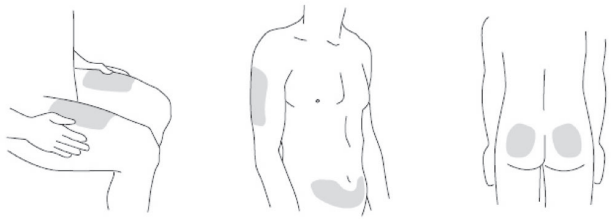
Figure A



Step 1: Prepare the injection.
- Choose a well-lit, clean, flat work surface.
- Wash your hands well with soap and warm water.

Step 2: Prepare your injection site
- Choose an injection site around your stomach area (abdomen), buttocks, and upper legs (thighs).
  If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(See Figure B)**
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give your injection.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

Figure B



*Areas in gray are recommended injection sites.

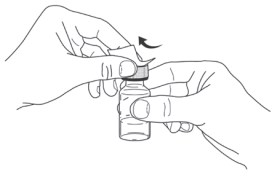
Step 3: Prepare the vial.
- Remove the cap from the top of the vial. Throw away the cap but do not remove the rubber stopper. **(See Figure C)**

Figure C



- Clean the rubber stopper with an antiseptic swab. **(See Figure D)**

Figure D

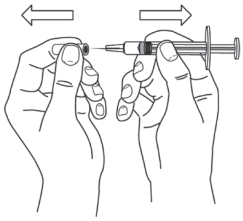


- Do not touch the rubber stopper after you clean it.
- Put the vial on a flat surface.

Step 4: Prepare the needle

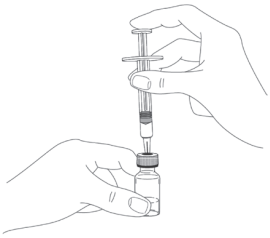
- Pick up the syringe with the needle attached.
- Remove the cap that covers the needle. **(See Figure E)**
- Throw the needle cap away. Do not touch the needle or allow the needle to touch anything.

Figure E



- Carefully pull back on the plunger to the line that matches the dose prescribed by your doctor.
- Hold the vial between your thumb and index (pointer) finger.
- Use your other hand to push the syringe needle through the center of the rubber stopper. **(See Figure F)**

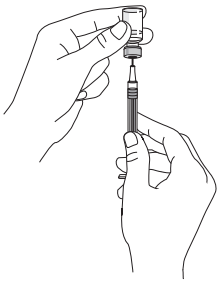
Figure F



- Push down on the plunger until all of the air has gone from the syringe into the vial.
- Turn the vial and the syringe upside down. **(See Figure G)**
- Hold the STELARA vial with one hand.
- It is important that the needle is always in the liquid in order to prevent air bubbles forming in the syringe.
- Pull back on the syringe plunger with your other hand.
- Fill the syringe until the black tip of the plunger lines up with the mark that matches your prescribed dose.

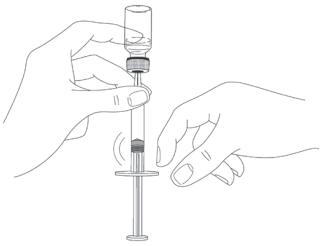
STELARA® (ustekinumab)

Figure G



- **Do not remove the needle from the vial.** Hold the syringe with the needle pointing up to see if it has any air bubbles inside.
- If there are air bubbles, gently tap the side of the syringe until the air bubbles rise to the top. **(See Figure H)**
- Slowly press the plunger up until all of the air bubbles are out of the syringe (but none of the liquid is out).
- Remove the syringe from the vial. Do not lay the syringe down or allow the needle to touch anything.

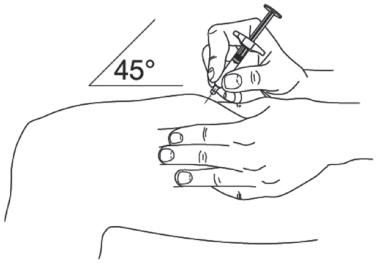
Figure H



Step 5: Inject STELARA

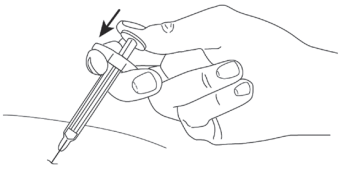
- Hold the barrel of the syringe in one hand, between the thumb and index fingers.
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure I)**

Figure I



- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched.
- When the syringe is empty, pull the needle out of your skin and let go of the skin. **(See Figure J)**

Figure J



- When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

If your dose is 90 mg, you will receive two 45 mg vials and you will need to give yourself a second injection right after the first. Repeat Steps 1-5 using a new syringe. Choose a different site for the second injection.

Step 6: Dispose of the needles and syringes.

- **Do not** re-use a syringe or needle.
- To avoid needle-stick injuries, do not recap a needle.
- Put your needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant,
  - and properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your sharps disposal container.
- Throw away the vial into the container where you put the syringes and needles.
- If you have any questions, talk to your doctor or pharmacist.

Keep STELARA and all medicines out of the reach of children.

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US
License No. 1864 at Cilag AG, Schaffhausen, Switzerland

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 10/2017

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cp-59529v1

https://web.archive.org/web/20170212011712/http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/761044Orig1s000ltr.pdf

BLA 761044

BLA APPROVAL

Janssen Biotech, Inc.
Attention: Joseph Lallier
Associate Director, Global Regulatory Affairs
1400 McKean Road
P.O. Box 776
Spring House, PA 19477

Dear Mr. Lallier:

Please refer to your Biologics License Application (BLA) dated November 25, 2015, received November 25, 2015, submitted under section 351(a) of the Public Health Service Act for STELARA (ustekinumab) Injection 130 mg/26 mL.

LICENSING

We have approved your BLA for STELARA (ustekinumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, STELARA under your existing Department of Health and Human Services U.S. License No. 1864. STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker, or failed or were intolerant to treatment with one or more TNF blockers.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ustekinumab drug substance at Janssen Biologics B.V., Leiden, Einsteinweg 101, 2333 CB Leiden, The Netherlands and Janssen Biologics (Ireland), Barnahely, Ringaskiddy Co., Cork, Ireland. The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4) . You may label your product with the proprietary name, STELARA, and will market it in 130 mg/26 mL Injection in single-dose vials.

DATING PERIOD

The dating period for STELARA shall be 24 months from the date of manufacture when stored at 2 – 8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of STELARA to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of STELARA, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, the patient package insert, and the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission

"**Final Printed Carton and Container Labels for approved BLA 761044**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for STELARA was not referred to a FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because an orphan designation was granted for your pediatric indication, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of malignancy and a known serious risk of opportunistic infections (such as tuberculosis [TB])

Furthermore, FDA has determined that the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess the known serious risks of malignancy and specific opportunistic infections (such as tuberculosis [TB]).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3112-1 Conduct a long-term, postmarketing, observational study to assess the long-term safety of STELARA (ustekinumab) versus other therapies used in the treatment of adults with moderate to severe Crohn's disease. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (e.g., tuberculosis [TB]). Specify concise case definitions, and provide

outcome validation for both primary and secondary outcomes. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to ustekinumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate, with a pre-specified statistical analysis method. For the ustekinumab-exposed and comparator(s), the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure adequate number of patients with at least 18 months of ustekinumab exposure at the end of the study. Follow for a period of at least 7 years.

The timetable you submitted on September 22, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	February 2017
Final Protocol Submission:	September 2017
Interim Report:	December 2025
Study Completion:	August 2029
Final Report Submission:	August 2030

Submit the protocol(s) to your IND 011632, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3112-2 Conduct a dose-ranging trial to determine the pharmacokinetics/pharmacodynamics, safety, and tolerability of STELARA (ustekinumab) induction dosing in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease despite conventional therapy.

The timetable you submitted on September 20, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2016
Study Completion:	February 2019
Final Report Submission:	August 2019

3112-3 Conduct a randomized, controlled, blinded, multicenter trial to evaluate the safety and efficacy of STELARA (ustekinumab) in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease despite conventional therapy.

The timetable you submitted on September 22, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	December 2019
Final Protocol Submission:	June 2020
Study Completion:	February 2024
Final Report Submission:	September 2024

3112-4 Conduct a clinical trial to assess whether STELARA (ustekinumab) alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in Crohn's disease (CD) patients treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs).

The timetable you submitted on September 7, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2017
Trial Completion:	September 2019
Final Report Submission:	March 2020

Submit clinical protocols to your IND 011632 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**,"

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"**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).
You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

If you have any questions, call Lawrence Allan, Regulatory Project Manager, at (240) 402 – 2786.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
09/23/2016

https://web.archive.org/web/20170225220025/http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761044lbl.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STELARA® safely and effectively. See full prescribing information for STELARA®.

STELARA® (ustekinumab) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage, Crohn's Disease (1.3)	09/2016
Dosage and Administration (2.3)	09/2016
Dosage and Administration (2.6)	09/2016

----------INDICATIONS AND USAGE----------

STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of adult patients with:

- *moderate to severe plaque psoriasis (Ps)* who are candidates for phototherapy or systemic therapy. (1.1)
- *active psoriatic arthritis (PsA)*, alone or in combination with methotrexate. (1.2)
- *moderately to severely active Crohn's disease (CD)* who have
  - failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker or
  - failed or were intolerant to treatment with one or more TNF blockers. (1.3)

----------DOSAGE AND ADMINISTRATION----------

Psoriasis Recommended Adult Subcutaneous Dosage (2.1):

Weight Range (kilogram)	Dosage Regimen
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks

Psoriatic Arthritis Recommended Adult Subcutaneous Dosage (2.2):

- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Crohn's Disease Recommended Initial Adult Intravenous Dosage (2.3):
A single intravenous infusion using weight-based dosing:

Weight Range (kilogram)	Recommended Dosage
Up to 55 kg	260 mg (2 vials)
Greater than 55 kg to 85 kg	390 mg (3 vials)
Greater than 85 kg	520 mg (4 vials)

Crohn's Disease Recommended Maintenance Adult Subcutaneous Dosage (2.3):
A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

----------DOSAGE FORMS AND STRENGTHS----------

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL in a single-dose prefilled syringe (3)
- Injection: 45 mg/0.5 mL in a single-dose vial (3)

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------

Clinically significant hypersensitivity to ustekinumab or to any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing STELARA® until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STELARA®. Initiate treatment of latent TB before administering STELARA®. (5.3)
- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur. (5.5)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA®. (5.6)

----------ADVERSE REACTIONS----------

Most common adverse reactions are:

- Psoriasis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)
- Crohn's Disease, induction (≥3%): vomiting. (6.1)
- Crohn's Disease, maintenance (≥3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 1.2 Psoriatic Arthritis (PsA)
- 1.3 Crohn's Disease

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- 2.1 Psoriasis
- 2.2 Psoriatic Arthritis
- 2.3 Crohn's Disease
- 2.4 General Considerations for Administration
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4 CONTRAINDICATIONS

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- 5.2 Theoretical Risk for Vulnerability to Particular Infections
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- 7.3 CYP450 Substrates
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Reference ID: 3990240

8 USE IN SPECIFIC POPULATIONS
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8.4 Pediatric Use
8.5 Geriatric Use
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11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Psoriasis (Ps)

STELARA® is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

STELARA® is indicated for the treatment of adult patients with active psoriatic arthritis. STELARA® can be used alone or in combination with methotrexate (MTX).

1.3 Crohn's Disease

STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have:

- failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker or
- failed or were intolerant to treatment with one or more TNF blockers.

2 DOSAGE AND ADMINISTRATION

2.1 Psoriasis

Subcutaneous Adult Dosage Regimen

- For patients weighing 100 kg or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

In subjects weighing more than 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects *[see Clinical Studies (14)]*.

2.2 Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

2.3 Crohn's Disease

Intravenous Induction Adult Dosage Regimen

A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 1 *[see Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)]*.

Table 1: Initial Intravenous Dosage of STELARA®

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4

Subcutaneous Maintenance Adult Dosage Regimen

The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

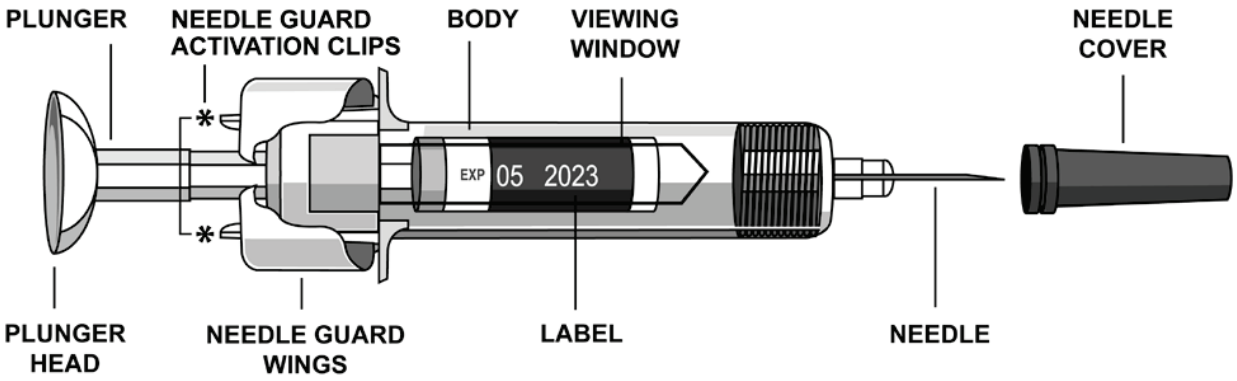
2.4 General Considerations for Administration

- After proper training in subcutaneous injection technique, a patient may self-inject with STELARA® if a physician determines that it is appropriate. Patients should be instructed to follow the directions provided in the Medication Guide *[see Medication Guide]*.
- The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The needle cover should not be handled by persons sensitive to latex.
- It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated. When using the single-dose vial, a 27 gauge, ½ inch needle is recommended.
- STELARA® is intended for use under the guidance and supervision of a physician. STELARA® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.
- Prior to administration, visually inspect STELARA® for particulate matter and discoloration. STELARA® is clear, colorless to light yellow and may contain a few small translucent or white particles. Do not use STELARA® if it is discolored or cloudy, or if other particulate matter is present. STELARA® does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

2.5 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard

Refer to the diagram below for the provided instructions.

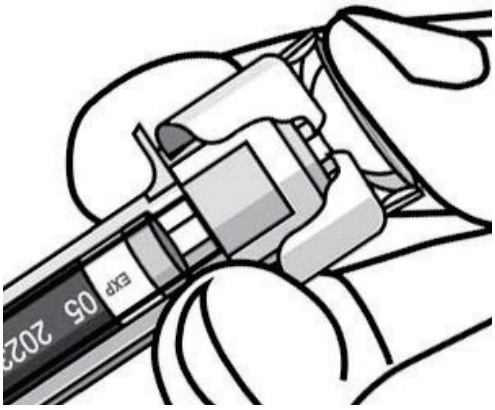
To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.



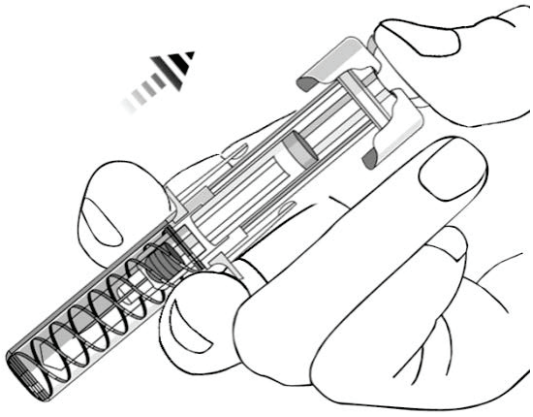
- Hold the BODY and remove the NEEDLE COVER. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE COVER or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE COVER in place**.

- Inject STELARA® subcutaneously as recommended *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

- Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the needle guard wings. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard**.



- After injection, maintain the pressure on the PLUNGER HEAD and remove the needle from the skin. Slowly take your thumb off the PLUNGER HEAD to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by the illustration below:



- Used syringes should be placed in a puncture-resistant container.

2.6 Preparation and Administration of STELARA® 130 mg/26 mL (5 mg/mL) Vial for Intravenous Infusion (Crohn's Disease)

STELARA® solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA® vials needed based on patient weight (Table 1). Each 26 mL vial of STELARA® contains 130 mg of ustekinumab.

2. Withdraw, and then discard a volume of the 0.9% Sodium Chloride Injection, USP from the 250 mL infusion bag equal to the volume of STELARA® to be added (discard 26 mL sodium chloride for each vial of STELARA® needed, for 2 vials- discard 52 mL, for 3 vials- discard 78 mL, 4 vials- discard 104 mL).

3. Withdraw 26 mL of STELARA® from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.

4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion solution may be stored for up to four hours prior to infusion.

6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).

7. Do not infuse STELARA® concomitantly in the same intravenous line with other agents.

8. STELARA® does not contain preservatives. Each vial is for single use only. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be stored for up to 4 hours at room temperature up to 25°C (77°F). Do not freeze. Discard any unused portion of the infusion solution.

3 DOSAGE FORMS AND STRENGTHS

STELARA® (ustekinumab) is colorless to slightly yellow solution.

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL in a single-dose vial

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

STELARA® is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

STELARA® may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in subjects receiving STELARA® *[see Adverse Reactions (6.1)]*.

Serious infections requiring hospitalization occurred in patients with psoriasis, psoriatic arthritis and Crohn's disease in clinical studies. In patients with psoriasis, serious infections included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections. In patients with psoriatic arthritis, serious infections included cholecystitis. In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, ophthalmic herpes, pneumonia, and listeria meningitis.

Treatment with STELARA® should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STELARA® in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with STELARA® and consider discontinuing STELARA® for serious or clinically significant infections until the infection resolves or is adequately treated.

5.2 Theoretical Risk for Vulnerability to Particular Infections

Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances.

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis infection prior to initiating treatment with STELARA®.

Do not administer STELARA® to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering STELARA®. Consider anti-tuberculosis therapy prior to initiation of STELARA® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving STELARA® for signs and symptoms of active tuberculosis during and after treatment.

5.4 Malignancies

STELARA® is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA® in clinical studies *[see Adverse Reactions (6.1)]*. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy *[see Nonclinical Toxicology (13)]*.

The safety of STELARA® has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

There have been post marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving STELARA® who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving STELARA® should be monitored for the appearance of non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely *[see Adverse Reactions (6.1)]*.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with STELARA® *[see Adverse Reactions (6.1, 6.3)]*. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®.

5.6 Reversible Posterior Leukoencephalopathy Syndrome

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed in clinical studies of psoriasis and psoriatic arthritis. The subject, who had received 12 doses of STELARA® over approximately two years, presented with headache, seizures and confusion. No additional STELARA® injections were administered and the subject fully recovered with appropriate treatment. No cases of RPLS were observed in clinical studies of Crohn's disease.

RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported.

If RPLS is suspected, administer appropriate treatment and discontinue STELARA®.

5.7 Immunizations

Prior to initiating therapy with STELARA®, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with STELARA® should not receive live vaccines. BCG vaccines should not be given during treatment with STELARA® or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving STELARA® because of the potential risk for shedding from the household contact and transmission to patient.

Non-live vaccinations received during a course of STELARA® may not elicit an immune response sufficient to prevent disease.

5.8 Concomitant Therapies

In clinical studies of psoriasis the safety of STELARA® in combination with other immunosuppressive agents or phototherapy was not evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone *[see Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Psoriasis

The safety data reflect exposure to STELARA® in 3117 psoriasis subjects, including 2414 exposed for at least 6 months, 1855 exposed for at least one year, 1653 exposed for at least two years, 1569 exposed for at least three years, 1482 exposed for at least four years and 838 exposed for at least five years.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the STELARA® groups than the placebo group during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14)]*.

Table 2: Adverse reactions reported by ≥1% of subjects through Week 12 in Ps STUDY 1 and Ps STUDY 2

		STELARA®	
	Placebo	**45 mg**	**90 mg**
Subjects treated	**665**	**664**	**666**
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

Adverse reactions that occurred at rates less than 1% in the controlled period of Ps STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

One case of RPLS occurred during clinical studies *[see Warnings and Precautions (5.6)]*.

Infections

In the placebo-controlled period of clinical studies of psoriasis subjects (average follow-up of 12.6 weeks for placebo-treated subjects and 13.4 weeks for STELARA®-treated subjects), 27% of STELARA®-treated subjects reported infections (1.39 per subject-year of follow-up) compared with 24% of placebo-treated subjects (1.21 per subject-year of follow-up). Serious infections occurred in 0.3% of STELARA®-treated subjects (0.01 per subject-year of follow-up) and in 0.4% of placebo-treated subjects (0.02 per subject-year of follow-up) *[see Warnings and Precautions (5.1)]*.

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years), representing 8998 subject-years of exposure, 72.3% of STELARA®-treated subjects reported infections (0.87 per subject-years of follow-up). Serious infections were reported in 2.8% of subjects (0.01 per subject-years of follow-up).

Malignancies

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years, representing 8998 subject-years of exposure), 1.7% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of STELARA®-treated subjects (0.52 per hundred subject-years of follow-up) *[see Warnings and Precautions (5.4)]*. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical studies were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in STELARA®-treated patients during the controlled and uncontrolled portions of studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender and race).[1]

Psoriatic Arthritis

The safety of STELARA® was assessed in 927 patients in two randomized, double-blind, placebo-controlled studies in adult patients with active psoriatic arthritis (PsA). The overall safety profile of STELARA® in patients with PsA was consistent with the safety profile seen in psoriasis clinical studies. A higher incidence of arthralgia, nausea, and dental infections was observed in STELARA®-treated patients when compared with placebo-treated patients (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo-controlled portions of the PsA clinical studies.

Crohn's Disease

The safety of STELARA® was assessed in 1407 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter studies. These 1407 patients included 40 patients who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In Studies CD-1 and CD-2 there were 470 patients who received STELARA® 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3)]*. Patients who were responders in either Study CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or placebo for 44 weeks in Study CD-3. Patients in these 3 studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX)], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's Disease *[see Clinical Studies (14.3)]*.

The overall safety profile of STELARA® was consistent with the safety profile seen in the psoriasis and psoriatic arthritis clinical studies. Common adverse reactions in Studies CD-1 and CD-2 and in Study CD-3 are listed in Tables 3 and 4, respectively.

Table 3: Common adverse reactions through Week 8 in Studies CD-1 and CD-2 occurring in ≥3% of STELARA®-treated patients and higher than placebo		
	Placebo **N=466**	**STELARA®** **6 mg/kg single intravenous induction dose** **N=470**
Vomiting	3%	4%

Other less common adverse reactions reported in patients in Studies CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 4: Common adverse reactions through Week 44 in Study CD-3 occurring in ≥3% of STELARA®-treated patients and higher than placebo		
	Placebo **N=133**	**STELARA®** **90 mg subcutaneous maintenance dose every 8 weeks** **N=131**
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

Infections

In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes were reported in one patient each.

Malignancies

With up to one year of treatment in the Crohn's disease clinical studies, 0.2% of STELARA®-treated patients (0.36 events per hundred patient-years) and 0.2% of placebo-treated patients (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.2% of STELARA®-treated patients (0.27 events per hundred patient-years) and in none of the placebo-treated patients.

Hypersensitivity Reactions Including Anaphylaxis

In CD studies, two patients reported hypersensitivity reactions following STELARA® administration. One patient experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of patients receiving subcutaneous STELARA®). In addition, one patient experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous

STELARA® dose (0.08% of patients receiving intravenous STELARA®). These patients were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour.

6.2 Immunogenicity

Approximately 6% of patients treated with STELARA® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titer. In Crohn's disease clinical studies, less than 3% of patients treated with STELARA® developed antibodies to ustekinumab. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen. No ustekinumab-related serious hypersensitivity reactions were observed in psoriasis, psoriatic arthritis and Crohn's disease clinical studies. In psoriasis studies, the majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

The data above reflect the percentage of subjects whose test results were positive for antibodies to ustekinumab and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ustekinumab with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval of STELARA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to STELARA® exposure.

Immune system disorders: Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria) *[see Warnings and Precautions (5.5)]*.

Skin reactions: Pustular psoriasis, erythrodermic psoriasis.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines with STELARA® *[see Warnings and Precautions (5.7)]*.

7.2 Concomitant Therapies

In psoriasis studies the safety of STELARA® in combination with immunosuppressive agents or phototherapy has not been evaluated *[see Warnings and Precautions (5.8)]*. In psoriatic arthritis studies, concomitant methotrexate use did not appear to influence the safety or efficacy of STELARA®. In Crohn's disease studies, immunomodulators (6-mercaptopurine, azathioprine, methotrexate) were used concomitantly in approximately 30% of patients and corticosteroids were used concomitantly in approximately 40% of patients. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of STELARA®.

7.3 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, STELARA®, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA® in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed *[see Clinical Pharmacology (12.3)]*.

7.4 Allergen Immunotherapy

STELARA® has not been evaluated in patients who have undergone allergy immunotherapy. STELARA® may decrease the protective effect of allergen immunotherapy (decrease tolerance) which may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergen immunotherapy, particularly for anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to STELARA® during pregnancy. Patients should be encouraged to enroll by calling 1-877-311-8972.

Risk Summary

Limited data on the use of STELARA® in pregnant women are insufficient to inform a drug associated risk *[see Data]*. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the human exposure at the maximum recommended human subcutaneous dose (MRHD).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Limited data on use of STELARA® in pregnant women from observational studies, published case reports, and postmarketing surveillance are insufficient to inform a drug associated risk.

Animal Data

Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks.

In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly at exposures greater than 100 times the human subcutaneous exposure from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab-related effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of ustekinumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ustekinumab was present in the milk of lactating monkeys administered ustekinumab. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Maternal IgG is known to be present in human milk. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule and is degraded in the gastrointestinal tract. However, if ustekinumab is transferred into human milk the effects of local exposure in the gastrointestinal tract are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STELARA® and any potential adverse effects on the breastfed child from STELARA® or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of STELARA® in pediatric patients have not been established.

8.5 Geriatric Use

Of the 5884 subjects exposed to STELARA®, a total of 306 were 65 years or older (183 patients with psoriasis, 65 patients with psoriatic arthritis and 58 with Crohn's disease), and 34 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

Single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for

any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, ustekinumab is produced in a well characterized recombinant cell line and is purified using standard bio-processing technology. The manufacturing process contains steps for the clearance of viruses. Ustekinumab is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to slightly yellow solution that may contain a few small translucent or white particles with pH of 5.7- 6.3.

STELARA® for Subcutaneous Use

Available as 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL, supplied as a sterile solution in a single-dose prefilled syringe with a 27 gauge fixed ½ inch needle and as 45 mg of ustekinumab in 0.5 mL in a single-dose 2 mL Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cover that contains dry natural rubber (a derivative of latex).

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

STELARA® for Intravenous Infusion

Available as 130 mg of ustekinumab in 26 mL, supplied as a single-dose 30 mL Type I glass vial with a coated stopper.

Each 26 mL vial delivers 130 mg ustekinumab, EDTA disodium salt dihydrate (0.52 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's Disease. In animal models of colitis, genetic absence

or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

12.2 Pharmacodynamics

In a small exploratory study, a decrease was observed in the expression of mRNA of its molecular targets IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to two weeks post-treatment in subjects with psoriasis.

12.3 Pharmacokinetics

Absorption

In subjects with psoriasis, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in subjects with psoriasis.

Following multiple subcutaneous doses of STELARA® in patients with psoriasis, the steady-state serum concentrations of ustekinumab were achieved by Week 28. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease, following the recommended intravenous induction dose, mean peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL. Starting at Week 8, the recommended subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in ustekinumab concentration over time when given subcutaneously every 8 weeks. Mean steady-state trough concentration was 2.51 ± 2.06 mcg/mL for 90 mg ustekinumab administered every 8 weeks.

Distribution

In a population pharmacokinetic analysis of ustekinumab, the volume of distribution of the central compartment was 2.74 L (95% CI: 2.69, 2.78), and the total volume of distribution at steady-state was 4.62 L in patients with Crohn's disease.

Elimination

The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following subcutaneous administration. In a population pharmacokinetic analysis of ustekinumab, the clearance was 0.19 L/day (95% CI: 0.185, 0.197) with an estimated median terminal half-life of approximately 19 days in patients with Crohn's disease.

Metabolism

The metabolic pathway of ustekinumab has not been characterized. As a human IgG1κ monoclonal antibody ustekinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Specific Populations

Weight

When given the same dose, subjects with psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of higher weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group.

Age: Geriatric Population

A population pharmacokinetic analysis (N=106/1937 patients with psoriasis greater than or equal to 65 years old) was performed to evaluate the effect of age on the pharmacokinetics of ustekinumab. There were no apparent changes in pharmacokinetic parameters (clearance and volume of distribution) in subjects older than 65 years old.

Drug Interaction Studies

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). However, the clinical relevance of *in vitro* data has not been established *[see Drug Interactions (7.3)]*.

No *in vivo* drug interaction studies have been conducted with STELARA®.

Population pharmacokinetic data analyses indicated that the clearance of ustekinumab was not impacted by concomitant MTX, NSAIDs, and oral corticosteroids, or prior exposure to a TNF blocker in patients with psoriatic arthritis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of STELARA®. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, prior to and during early pregnancy.

13.2 Animal Toxicology and/or Pharmacology

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection.

14 CLINICAL STUDIES

14.1 Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled studies (Ps STUDY 1 and Ps STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies.

Ps STUDY 1 enrolled 766 subjects and Ps STUDY 2 enrolled 1230 subjects. The studies had the same design through Week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of STELARA®. Subjects randomized to STELARA® received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA® (either 45 mg or 90 mg) at Weeks 12 and 16.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

In both studies, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in Ps STUDY 1 and 40% of subjects in Ps STUDY 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of subjects had a history of psoriatic arthritis.

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 5 below.

Table 5: Clinical Outcomes Ps STUDY 1 and Ps STUDY 2

Week 12	**Ps STUDY 1**			**Ps STUDY 2**		
		STELARA®			**STELARA®**	
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Subjects randomized	255	255	256	410	409	411
PASI 75 response	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PGA of Cleared or Minimal	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)

Examination of age, gender, and race subgroups did not identify differences in response to STELARA® among these subgroups.

In subjects who weighed 100 kg or less, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 6 below).

Table 6: Clinical Outcomes by Weight Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			Ps STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response at Week 12*						
≤100 kg	4%	74%	65%	4%	73%	78%
	6/166	124/168	107/164	12/290	218/297	225/289
>100 kg	2%	54%	68%	3%	49%	71%
	2/89	47/87	63/92	3/120	55/112	86/121
PGA of Cleared or Minimal at Week 12*						
≤100 kg	4%	64%	63%	5%	74%	75%
	7/166	108/168	103/164	14/290	220/297	216/289
>100 kg	3%	49%	58%	3%	51%	69%
	3/89	43/87	53/92	4/120	57/112	84/121

* Patients were dosed with study medication at Weeks 0 and 4.

Subjects in Ps STUDY 1 who were PASI 75 responders at both Weeks 28 and 40 were re-randomized at Week 40 to either continued dosing of STELARA® (STELARA® at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to STELARA® treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks.

14.2 Psoriatic Arthritis

The safety and efficacy of STELARA® was assessed in 927 patients (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled studies in adult patients 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Patients were randomized to receive treatment with STELARA® 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)-α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the patients

had been previously treated with TNF blocker, of whom over 70% had discontinued their TNF blocker treatment for lack of efficacy or intolerance at any time.

Clinical Response

In both studies, a greater proportion of patients achieved ACR 20, ACR 50 and PASI 75 response in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 7). ACR 70 responses were also higher in the STELARA® 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in STUDY 2. Responses were similar in patients regardless of prior TNFα exposure.

Table 7: ACR 20, ACR 50, ACR 70 and PASI 75 responses in PsA STUDY 1 and PsA STUDY 2 at Week 24

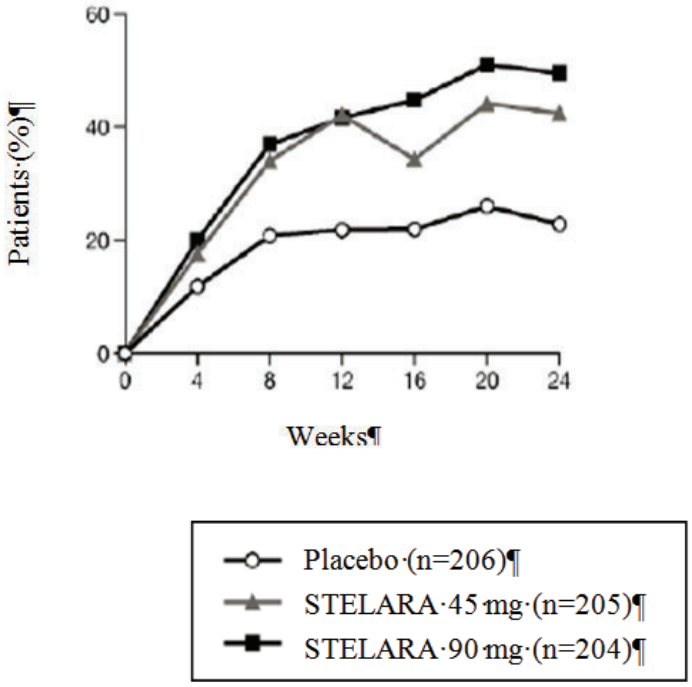
	PsA STUDY 1			PsA STUDY 2		
		STELARA®			STELARA®	
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Number of patients randomized	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)	7 (7%)	18 (17%)	24 (23%)
ACR 70 response, N (%)	5 (2%)	25 (12%)	29 (14%)	3 (3%)	7 (7%)	9 (9%)
Number of patients with ≥ 3% BSA[a]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)

[a] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

The percent of patients achieving ACR 20 responses by visit is shown in Figure 1.

Figure 1: Percent of patients achieving ACR 20 response through Week 24

PsA STUDY 1



The results of the components of the ACR response criteria are shown in Table 8.

Table 8: Mean change from baseline in ACR components at Week 24

	PsA STUDY 1		
		STELARA®	
	Placebo (N=206)	**45 mg (N= 205)**	**90 mg (N= 204)**
Number of swollen joints[a]			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints[b]			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Patient's assessment of pain[c]			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Patient global assessment[c]			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment[c]			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1

Disability index (HAQ)[d]			
Baseline	1.2	1.2	1.2
Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)[e]			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

[a] Number of swollen joints counted (0-66)

[b] Number of tender joints counted (0-68)

[c] Visual analogue scale; 0= best, 10=worst.

[d] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[e] CRP: (Normal Range 0.0-1.0 mg/dL)

An improvement in enthesitis and dactylitis scores was observed in each STELARA® group compared with placebo at Week 24.

Physical Function

STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by HAQ-DI at Week 24. In both studies, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24.

14.3 Crohn's Disease

STELARA® was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy.

Studies CD-1 and CD-2

In studies CD-1 and CD-2, 1409 patients were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, patients were randomized to receive a single intravenous administration of STELARA® at either approximately 6 mg/kg, placebo (see Table 1), or 130 mg (a lower dose than recommended).

In Study CD-1, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 319 in the STELARA® approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator (6-mercaptopurine, azathioprine, methotrexate; 68% of patients), or both (49% of patients). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 286 in the STELARA® and 290 in the placebo group.

In these induction studies, a greater proportion of patients treated with STELARA® achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 9 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in STELARA® treated patients and continued to improve through Week 8.

Table 9: Induction of Clinical Response and Remission in CD-1* and CD-2**

	CD-1 n=741			CD-2 n=627		
	Placebo N=247	**STELARA®† N=249**	**Treatment difference and 95% CI**	**Placebo N=209**	**STELARA®† N=209**	**Treatment difference and 95% CI**
Clinical Response (100 point), Week 6	53 (21%)	84 (34%)[a]	12% (4%, 20%)	60 (29%)	116 (56%)[b]	27% (18%, 36%)
Clinical Remission, Week 8	18 (7%)	52 (21%)[b]	14% (8%, 20%)	41 (20%)	84 (40%)[b]	21% (12%, 29%)
Clinical Response (100 point), Week 8	50 (20%)	94 (38%)[b]	18% (10%, 25%)	67 (32%)	121 (58%)[b]	26% (17%, 35%)
70 Point Response, Week 6	75 (30%)	109 (44%)[a]	13% (5%, 22%)	81 (39%)	135 (65%)[b]	26% (17%, 35%)
70 Point Response, Week 3	67 (27%)	101 (41%)[a]	13% (5%, 22%)	66 (32%)	106 (51%)[b]	19% (10%, 28%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission: 70 point response is defined as reduction in CDAI score by at least 70 points

* Patient population consisted of patients who failed or were intolerant to TNF blocker therapy

** Patient population consisted of patients who failed or were intolerant to corticosteroids or immunomodulators (e.g., 6-mercaptopurine, azathioprine, methotrexate) and previously received but not failed a TNF blocker or were never treated with a TNF blocker.

† Infusion dose of STELARA® using the weight-based dosage regimen specified in Table 1.

[a] $0.001 \leq p < 0.01$

[b] $p < 0.001$

Study CD-3

The maintenance study (CD-3), evaluated 388 patients who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 of induction with STELARA® in studies CD-1 or CD-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks or placebo for 44 weeks (see Table 10).

Table 10: Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose)			
	Placebo* **N=131†**	**90 mg STELARA® every 8 weeks** **N=128†**	**Treatment difference and 95% CI**
Clinical Remission	47 (36%)	68 (53%)[a]	17% (5%, 29%)
Clinical Response	58 (44%)	76 (59%)[b]	15% (3%, 27%)
Clinical Remission in patients in remission at the start of maintenance therapy**	36/79 (46%)	52/78 (67%)[a]	21% (6%, 36%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to STELARA® and were randomized to receive placebo at the start of maintenance therapy.

** Patients in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.

† Patients who achieved clinical response to STELARA® at the end of the induction study.

[a] $p < 0.01$

[b] $0.01 \leq p < 0.05$

At Week 44, 47% of patients who received STELARA® were corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group.

At Week 0 of Study CD-3, 34/56 (61%) STELARA® treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44.

At Week 0 of Study CD-3, 46/72 (64%) STELARA® treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of STELARA® treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

Patients who were not in clinical response 8 weeks after STELARA® induction were not included in the primary efficacy analyses for Study CD-3; however, these patients were eligible to receive a 90 mg subcutaneous injection of STELARA® upon entry into Study CD-3. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

15 REFERENCES

1 Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 6.6.2 Regs Research Data, Nov 2009 Sub (1973-2007) - Linked To County Attributes - Total U.S., 1969-2007 Counties, National Cancer

Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2010, based on the November 2009 submission.

16 HOW SUPPLIED/STORAGE AND HANDLING

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to slightly yellow solution. STELARA® is available in single-dose prefilled syringes containing 45 mg or 90 mg or single-dose vials containing 45 mg of ustekinumab for subcutaneous use. Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber.

STELARA® is also available in single-dose vials containing 130 mg ustekinumab for intravenous use.

Subcutaneous Use	**NDC**
45 mg/0.5 mL single-dose prefilled syringe	57894-060-03
90 mg/mL single-dose prefilled syringe	57894-061-03
45 mg/0.5 mL single-dose vial	57894-060-02
Intravenous Infusion	**NDC**
130 mg/26 mL (5 mg/mL) single-dose vial	57894-054-27

Storage and Stability

STELARA® vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store STELARA® vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use)

Infections

Inform patients that STELARA® may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients of the risk of developing malignancies while receiving STELARA® *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

- Advise patients to seek immediate medical attention if they experience any signs or symptoms of serious hypersensitivity reactions and discontinue STELARA® *[see Warnings and Precautions (5.5)]*.

- Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex *[see Dosage and Administration (2.4)]*

Immunizations

Inform patients that STELARA® can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions (5.7)]*.

Pregnancy Registry

Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to STELARA® *[see Use in Specific Populations (8.1)]*.

Administration

Instruct patients to follow sharps disposal recommendations, as described in the Instructions for Use.

Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Cilag AG, Schaffhausen, Switzerland

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MEDICATION GUIDE
STELARA (stel ar' a)
(ustekinumab)
injection, for subcutaneous or intravenous use

What is the most important information I should know about STELARA?

STELARA is a medicine that affects your immune system. STELARA can increase your risk of having serious side effects, including:

Serious infections: STELARA may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections while taking STELARA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.

- Your doctor should check you for TB before starting STELARA.
- If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with STELARA and during treatment with STELARA.
- Your doctor should watch you closely for signs and symptoms of TB during treatment with STELARA.

You should not start taking STELARA if you have any kind of infection unless your doctor says it is okay.

Before starting STELARA, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have TB, or have been in close contact with someone with TB.

After starting STELARA, call your doctor right away if you have any symptoms of an infection (see above). STELARA can make you more likely to get infections or make an infection that you have worse. People who have a genetic problem where the body does not make any of the proteins interleukin 12 (IL-12) and interleukin 23 (IL-23) are at a higher risk for certain serious infections. These infections can spread throughout the body and cause death. People who take STELARA may also be more likely to get these infections.

Cancers

STELARA may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your doctor if you have ever had any type of cancer. Some people who are receiving STELARA and have risk factors for skin cancer have developed certain types of skin cancers. During your treatment with STELARA, tell your doctor if you develop any new skin growths.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS):

RPLS is a rare condition that affects the brain and can cause death. The cause of RPLS is not known. If RPLS is found early and treated, most people recover. Tell your doctor right away if you have any new or worsening medical problems including:

- headache
- seizures
- confusion
- vision problems

What is STELARA?

STELARA is a prescription medicine used to treat adults 18 years and older with:

- moderate or severe psoriasis that involves large areas or many areas of their body, who may benefit

from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).

- active psoriatic arthritis. STELARA can be used alone or with methotrexate.
- moderately to severely active Crohn's disease in people who have already taken other medicine that did not work well enough or they could not tolerate it.

STELARA may improve your psoriasis, psoriatic arthritis or Crohn's disease, but may also lower the ability of your immune system to fight infections. Taking STELARA may also increase your risk for certain types of cancer.

It is not known if STELARA is safe and effective in children.

Do not take STELARA if you are allergic to ustekinumab or any of the ingredients in STELARA. See the end of this Medication Guide for a complete list of ingredients in STELARA.

Before you receive STELARA, tell your doctor if you:

- have any of the conditions or symptoms listed in the section "**What is the most important information I should know about STELARA**?"
- ever had an allergic reaction to STELARA. Ask your doctor if you are not sure.
- are allergic to latex. The needle cover on the prefilled syringe contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who take STELARA should not receive live vaccines. Tell your doctor if anyone in your house needs a vaccine. The viruses used in some types of vaccines can spread to people with a weakened immune system, and can cause serious problems. **You should not receive the BCG vaccine during the one year before taking STELARA or one year after you stop taking STELARA**.
- have any new or changing lesions within psoriasis areas or on normal skin.
- are receiving or have received allergy shots, especially for serious allergic reactions. Allergy shots may not work as well for you during treatment with STELARA. STELARA may also increase your risk of having an allergic reaction to an allergy shot.
- receive or have received phototherapy for your psoriasis.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if STELARA can harm your unborn baby. You and your doctor should decide if you will take STELARA. There is a pregnancy registry for women who take STELARA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you are pregnant or become pregnant while taking STELARA, talk to your doctor about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.
- are breastfeeding or plan to breastfeed. It is thought that STELARA passes into your breast milk in small amounts.
- Talk to your doctor about the best way to feed your baby if you take STELARA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use STELARA?

- Use STELARA exactly as prescribed by your doctor.
- **The needle cover on the STELARA prefilled syringe contains latex. Do not handle the needle cover if you are sensitive to latex.**
- Adults with Crohn's disease will receive the first dose of STELARA through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. It takes at least 1 hour to receive the full dose of medicine. You will then receive STELARA as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of STELARA, as described below.
- Adults with psoriasis or psoriatic arthritis will receive STELARA as an injection under the skin (subcutaneous injection) as described below.
- **Injecting STELARA under your skin**
  - If your doctor decides that you or a caregiver may give your injections of STELARA at home, you should receive training on the right way to prepare and inject STELARA. Do not try to inject STELARA yourself until you or your caregiver have been shown how to inject STELARA by your doctor or nurse.
  - Inject STELARA under the skin (subcutaneous injection) in your upper arms, buttocks, upper legs (thighs) or stomach area (abdomen).
  - Do not give an injection in an area of the skin that is tender, bruised, red or hard.
  - Use a different injection site each time you use STELARA.
  - If you inject more STELARA than prescribed, call your doctor right away.
  - Be sure to keep all of your scheduled follow-up appointments.
- **Read the detailed Instructions for Use at the end of this Medication Guide for instructions about how to prepare and inject a dose of STELARA, and how to properly throw away (dispose of) used needles and syringes.**

What should I avoid while using STELARA?

You should not receive a live vaccine while taking STELARA. See **"What should I tell my doctor before receiving STELARA?"**

What are the possible side effects of STELARA?

STELARA may cause serious side effects, including:

- See "**What is the most important information I should know about STELARA?**"
- **Serious allergic reactions.** Serious allergic reactions can occur with STELARA. Stop using STELARA and get medical help right away if you have any of the following symptoms of a serious allergic reaction:
  - feeling faint
  - swelling of your face, eyelids, tongue, or throat
  - chest tightness
  - skin rash

Common side effects of STELARA include:

- upper respiratory infections
- headache
- tiredness
- itching
- vomiting
- vaginal yeast infections
- urinary tract infections
- redness at the injection site

These are not all of the possible side effects of STELARA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Janssen Biotech, Inc. at 1-800 JANSSEN (1-800-526-7736).

How should I store STELARA?

- Store STELARA prefilled syringes in a refrigerator between 36°F to 46°F (2°C to 8°C).

- Store STELARA in the original carton to protect it from light until time to use it.
- Do not freeze STELARA.
- Do not shake STELARA.

Keep STELARA and all medicines out of the reach of children.

General information about the safe and effective use of STELARA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use STELARA for a condition for which it was not prescribed. Do not give STELARA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your doctor or pharmacist for information about STELARA that was written for health professionals.

What are the ingredients in STELARA?

Active ingredient: ustekinumab

Inactive ingredients: single-dose prefilled syringe contains L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, and sucrose. **Single-dose vial** contains L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80 and sucrose.

Manufactured by: Janssen Biotech , Inc., Horsham, PA 19044, US License No. 1864

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For more information, go to *www.stelarainfo.com* or call 1-800-JANSSEN (1-800-526-7736).

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 09 2016

INSTRUCTIONS FOR USE
STELARA (stel ar' a**)**
(ustekinumab)
injection, for subcutaneous use

Instructions for injecting STELARA using a prefilled syringe.

Read this Instructions for Use before you start using STELARA. Your doctor or nurse should show you how to prepare and give your injection of STELARA the right way.

If you cannot give yourself the injection:
- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

Do not try to inject STELARA yourself until you have been shown how to inject STELARA by your doctor, nurse or health professional.

Important information:
- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
  - If your dose is 45 mg, you will receive one 45 mg prefilled syringe.
  - If your dose is 90 mg, you will receive either one 90 mg prefilled syringe or two 45 mg prefilled syringes. **If you receive two 45 mg prefilled syringes for a 90 mg dose, you will need to give yourself two injections, one right after the other.**
- Check the expiration date on the pre-filled syringe and carton. If the expiration date has passed, do not use it. If the expiration date has passed call your doctor or pharmacist, or call 1-800-JANSSEN (1-800-526-7736) for help.
- Make sure the syringe is not damaged.
- **The needle cover on the prefilled syringe contains latex. Do not handle the needle cover on the STELARA prefilled syringe if you are sensitive to latex.**
- Check your prefilled syringe for any particles or discoloration. Your prefilled syringe should look clear and colorless to light yellow with few white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new prefilled syringe.
- **Do not shake the prefilled syringe at any time.** Shaking your prefilled syringe may damage your STELARA medicine. If your prefilled syringe has been shaken, do not use it. Get a new prefilled syringe.
- To reduce the risk of accidental needle sticks, each prefilled syringe has a needle guard that is automatically activated to cover the needle after you have given your injection. Do not pull back on the plunger at any time.

Gather the supplies you will need to prepare and to give your injection. (See Figure A)
You will need:
- antiseptic wipes
- cotton balls or gauze pads
- adhesive bandage

- your prescribed dose of STELARA **(See Figure B)**
- FDA-cleared sharps disposal container. **See "Step 4: Dispose of the syringe."**

Figure A

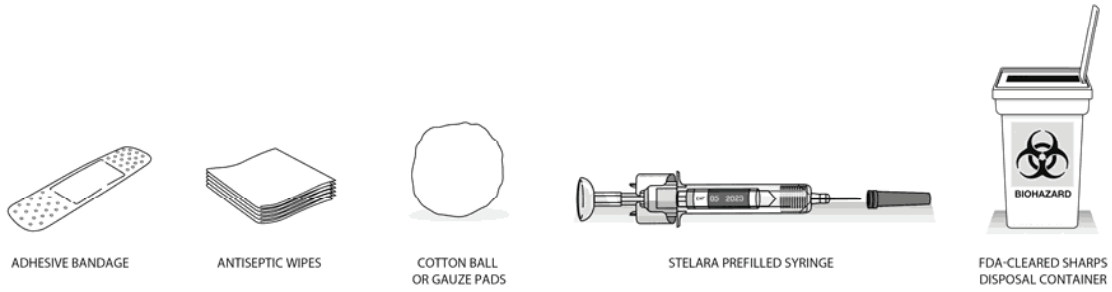
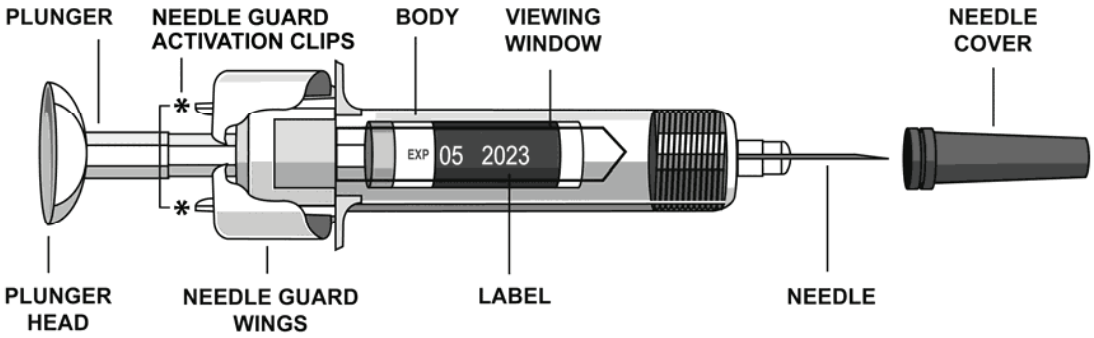


Figure B



Step 1: Prepare the injection.

- Choose a well lit, clean, flat work surface.
- Wash your hands well with soap and warm water.
- Hold the prefilled syringe with the covered needle pointing upward.

Step 2: Prepare your injection site

- Choose an injection site around your stomach area (abdomen), buttocks, upper legs (thighs). If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(See Figure C)**
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give your injection.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

Figure C

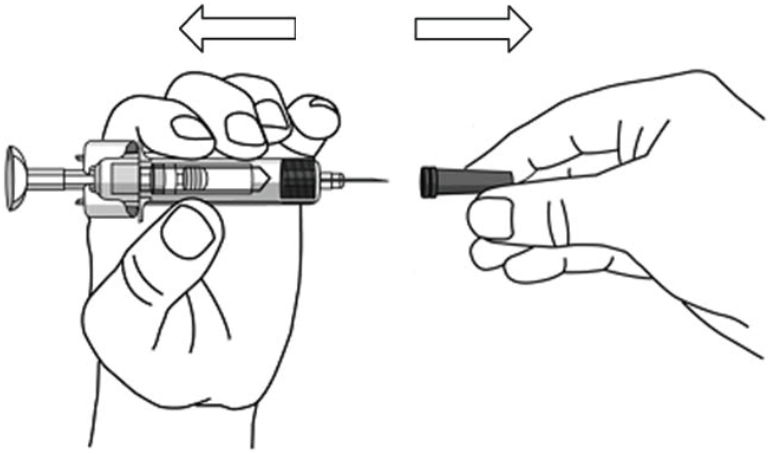


*Areas in gray are recommended injection sites.

Step 3: Inject STELARA

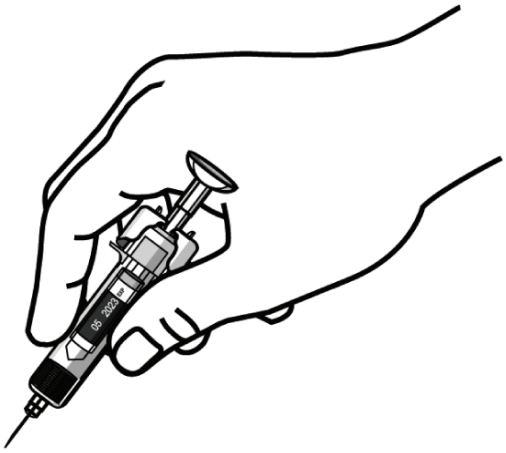
- Remove the needle cover when you are ready to inject your STELARA.
- **Do not** touch the plunger while removing the needle cover.
- Hold the body of the prefilled syringe with one hand, and pull the needle cover straight off. **(see Figure D)**
- Put the needle cover in the trash.
- You may also see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch the needle or let it touch anything.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place. Call your doctor, nurse or health professional for instructions.

Figure D



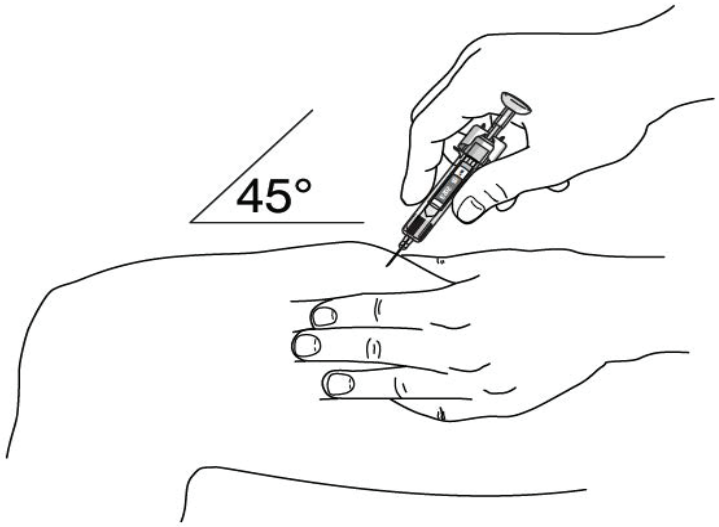
- Hold the body of the prefilled syringe in one hand between the thumb and index fingers. **(See Figure E)**

Figure E



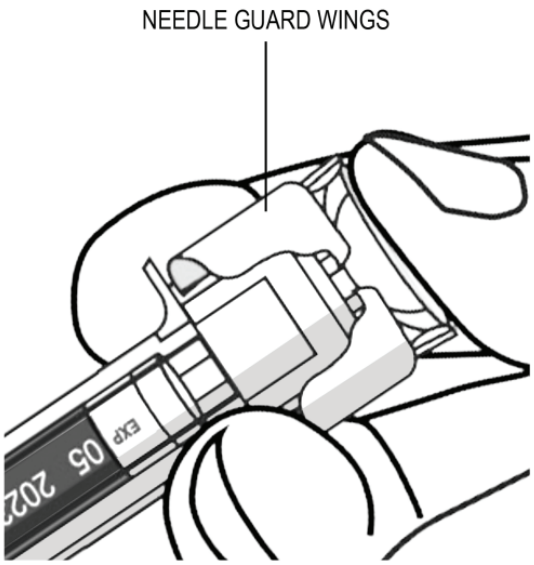
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure F)**

Figure F



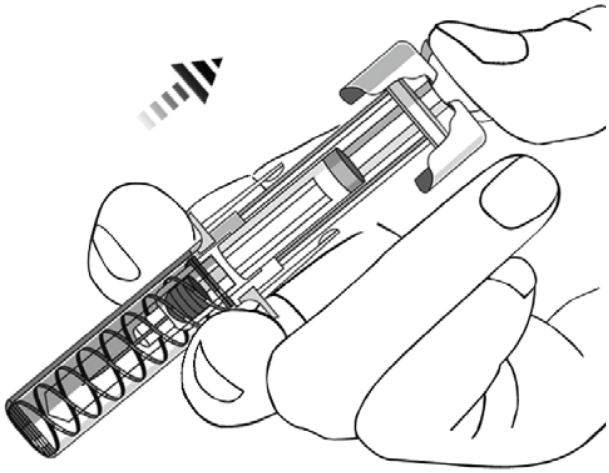
- Inject all of the liquid by using your thumb to push in the plunger until the plunger head is completely between the needle guard wings. **(See Figure G)**

Figure G



- When the plunger is pushed as far as it will go, keep pressure on the plunger head. Take the needle out of the skin and let go of the skin.
- Slowly take your thumb off the plunger head. This will let the empty syringe move up until the entire needle is covered by the needle guard. **(See Figure H)**

Figure H



- When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

Step 4: Dispose of the syringe.

- Put the syringe in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic.
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out.
  - upright and stable during use,
  - leak-resistant,
  - and properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your sharps disposal container.
- If you have any questions, talk to your doctor or pharmacist.

Keep STELARA and all medicines out of the reach of children.

Prefilled Syringe Manufactured by:
Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Issued 09/2016

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https://web.archive.org/web/20140708015840/http://general.takedapharm.com/content/file.aspx?filetypecode=ENTYVIOPI&CountryCode=US&LanguageCode=EN&cacheRandomizer=1489efd4-478b-47ea-b169-f720921b7a61

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENTYVIO safely and effectively. See full prescribing information for ENTYVIO.

ENTYVIO (vedolizumab) for injection, for intravenous use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

ENTYVIO is an integrin receptor antagonist indicated for:

Adult Ulcerative Colitis (UC) (1.1)

- Adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids:
  - inducing and maintaining clinical response
  - inducing and maintaining clinical remission
  - improving endoscopic appearance of the mucosa
  - achieving corticosteroid-free remission

Adult Crohn's Disease (CD) (1.2)

- Adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids:
  - achieving clinical response
  - achieving clinical remission
  - achieving corticosteroid-free remission

----------DOSAGE AND ADMINISTRATION----------

- Recommended dosage in UC and CD: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter. (2.3)
- Discontinue ENTYVIO in patients who do not show evidence of therapeutic benefit by Week 14. (2.3)
- Must reconstitute ENTYVIO lyophilized powder with Sterile Water for injection and must dilute in 250 mL of sterile 0.9% Sodium Chloride injection prior to administration. See Full Prescribing Information for complete reconstitution and dilution instructions. (2.4)
- Administer infusion solution within four hours of reconstitution and dilution. (2.4)
- Bring patients up to date with all immunizations (according to current immunization guidelines) before initiating treatment with ENTYVIO. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 300 mg of lyophilized vedolizumab in a single-use 20 mL vial. (3)

----------CONTRAINDICATIONS----------

Patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions (including anaphylaxis): Discontinue ENTYVIO if anaphylaxis or other serious allergic reactions occur. (5.1)
- Infections: Treatment with ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. (5.2)
- Progressive Multifocal Leukoencephalopathy: Although no cases have been observed in ENTYVIO clinical trials, JCV infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥3% and ≥1% higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adult Ulcerative Colitis

ENTYVIO (vedolizumab) is indicated for:

- inducing and maintaining clinical response,
- inducing and maintaining clinical remission,
- improving the endoscopic appearance of the mucosa, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

1.2 Adult Crohn's Disease

ENTYVIO (vedolizumab) is indicated for:

- achieving clinical response,
- achieving clinical remission, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Administer ENTYVIO as an intravenous infusion over 30 minutes. Do not administer as an intravenous push or bolus. ENTYVIO lyophilized powder must be reconstituted with Sterile Water for injection and diluted in 250 mL of sterile 0.9% Sodium Chloride injection prior to administration *[see Dosage and Administration (2.4)]*. After the infusion is complete, flush with 30 mL of sterile 0.9% Sodium Chloride injection.

ENTYVIO should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Observe patients during infusion and until the infusion is complete.

2.2 Prior to Administration of ENTYVIO

Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines.

2.3 Dosage in Adults with Ulcerative Colitis or Crohn’s Disease

The recommended dosage of ENTYVIO in adults with ulcerative colitis or Crohn's disease is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 14.

2.4 Reconstitution and Dilution Instructions

Reconstitution Instructions

Reconstitute ENTYVIO at room temperature. ENTYVIO should be reconstituted and prepared by a trained medical professional using aseptic technique by the following procedure:

1. Remove the flip-off cap from the single-dose vial and wipe with alcohol swab. Reconstitute ENTYVIO vial containing lyophilized powder with 4.8 mL of Sterile Water for injection, using a syringe with a 21 to 25 gauge needle.
2. Insert the syringe needle into the vial through the center of the stopper and direct the stream of Sterile Water for injection to the glass wall of the vial to avoid excessive foaming.
3. Gently swirl the vial for at least 15 seconds to dissolve the lyophilized powder. Do not vigorously shake or invert.
4. Allow the solution to sit for up to 20 minutes at room temperature to allow for reconstitution and for any foam to settle; the vial can be swirled and inspected for dissolution during this time. If not fully dissolved after 20 minutes, allow another 10 minutes for dissolution. Do not use the vial if the drug product is not dissolved within 30 minutes.
5. Visually inspect the reconstituted ENTYVIO solution for particulate matter and discoloration prior to administration. Solution should be clear or opalescent, colorless to light brownish yellow and free of visible particulates. Do not administer reconstituted solution showing uncharacteristic color or containing particulates.
6. Prior to withdrawing the reconstituted ENTYVIO solution from the vial, gently invert vial three times.
7. Withdraw 5 mL (300 mg) of reconstituted ENTYVIO solution using a syringe with a 21 to 25 gauge needle. Discard any remaining portion of the reconstituted solution in the vial.

Dilution Instructions

Add the 5 mL (300 mg) of reconstituted ENTYVIO solution to 250 mL of sterile 0.9% Sodium Chloride and gently mix the infusion bag. Do not add other medicinal products to the prepared infusion solution or intravenous infusion set. Once reconstituted and diluted, use the infusion solution as soon as possible.

Storage

If necessary, the infusion solution may be stored for up to four hours at 2° to 8°C (36º to 46ºF). Do not freeze. Discard any unused portion of the infusion solution**.**

3 DOSAGE FORMS AND STRENGTHS

ENTYVIO for injection: 300 mg of vedolizumab as a lyophilized cake in single dose 20 mL vials for reconstitution.

4 CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate) *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions and Hypersensitivity Reactions

In UC Trials I and II and CD Trials I and III, hypersensitivity reactions occurred including a case of anaphylaxis (one out of 1434 patients [0.07%]) *[see Adverse Reactions (6.1)]*. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to ENTYVIO may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment (e.g., epinephrine and antihistamines).

5.2 Infections

Patients treated with ENTYVIO are at increased risk for developing infections *[see Adverse Reactions (6.1)].* The most commonly reported infections in clinical trials occurring at a rate greater on ENTYVIO than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution when considering the use of ENTYVIO in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice. For progressive multifocal leukoencephalopathy (PML), see *Warnings and Precautions (5.3)*.

5.3 Progressive Multifocal Leukoencephalopathy

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised.

In ENTYVIO clinical trials, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. No claims of comparative safety to other integrin receptor antagonists can be made based on this data.

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue dosing permanently.

5.4 Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe

liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury *[see Adverse Reactions (6.1)]*.

5.5 Live and Oral Vaccines

Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines *[see Dosage and Administration (2.2)]*. Patients receiving ENTYVIO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following topics are also discussed in detail in the Warnings and Precautions section:

- Infusion-Related Reactions and Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.3)]*
- Liver Injury *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ENTYVIO in 3,326 patients and healthy volunteers in clinical trials, including 1,396 exposed for greater than one year, and 835 exposed for greater than two years.

The safety data described in *Table 1* are derived from four controlled Phase 3 trials (UC Trials I and II, and CD Trials I and III); data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included *[see Clinical Studies (14.1 and 14.2)]*.

In these trials, 1,434 patients received ENTYVIO 300 mg for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis and 962 patients had Crohn's disease. Patients were exposed for a mean duration of 259 days (UC Trials I and II) and 247 days (CD Trials I and III).

Adverse reactions were reported in 52% of patients treated with ENTYVIO and 45% of patients treated with placebo (UC Trials I and II: 49% with ENTYVIO and 37% with placebo; CD Trials I and III: 55% with ENTYVIO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with ENTYVIO compared to 4% of patients treated with placebo (UC Trials I and II: 8% with ENTYVIO and 7% with placebo; CD Trials I and III: 12% with ENTYVIO and 9%, with placebo).

The most common adverse reactions (reported by ≥3% of patients treated with ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and ≥1% higher than in combined placebo group) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain and pain in extremities (*Table 1*).

Table 1. Adverse Reactions in ≥3% of ENTYVIO-treated Patients and ≥1% Higher than in Placebo (UC Trials I and II* and CD Trials I and III*)

Adverse Reaction	ENTYVIO† (N=1434)	Placebo‡ (N=297)
Nasopharyngitis	13%	7%
Headache	12%	11%
Arthralgia	12%	10%
Nausea	9%	8%
Pyrexia	9%	7%
Upper respiratory tract infection	7%	6%
Fatigue	6%	3%
Cough	5%	3%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

*Data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

†Patients who received ENTYVIO for up to 52 weeks.

‡Patients who received placebo for up to 52 weeks.

Safety data for patients (n=279) in UC Trials I and II and CD Trials I and III who received ENTYVIO at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks, and for patients (n=416) in CD Trial II, a 10 week Crohn's disease trial, are similar to those listed in *Table 1*.

Infusion-Related Reactions and Hypersensitivity Reactions

Serious infusion-related reactions and hypersensitivity reactions including anaphylaxis have been reported following ENTYVIO administration in clinical trials *[see Warnings and Precautions (5.1)]*. In UC Trials I and II and Crohn's Trials I and III, one case of anaphylaxis [one out of 1434 patients treated with ENTYVIO (0.07%)] was reported by a Crohn's disease patient during the second infusion (symptoms reported were dyspnea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate) and was managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone.

In UC Trials I and II and CD Trials I and III, 4% of patients treated with ENTYVIO and 3% of patients treated with placebo experienced an infusion-related reaction (IRR). The most frequently observed IRR in the patients treated with ENTYVIO (reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting (each of these adverse reactions occurred in <1% in all patients treated with

ENTYVIO) and no individual adverse reaction reported occurred at a rate above 1%. These reactions generally occurred within the first two hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment. Less than 1% of patients treated with ENTYVIO had IRRs assessed by the investigator as severe, and IRRs requiring discontinuation of study treatment occurred in <1%.

In clinical trials, for patients with mild IRRs or hypersensitivity reactions, physicians were allowed to pretreat with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) prior to next infusion.

Infections

In UC Trials I and II and CD Trials I and III, the rate of infections was 0.85 per patient-year in the patients treated with ENTYVIO and 0.7 per patient-year in the patients treated with placebo *[see Warnings and Precautions (5.2)]*. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued ENTYVIO due to infections.

In UC Trials I and II and CD Trials I and III, the rate of serious infections was 0.07 per patient-year in patients treated with ENTYVIO and 0.06 per patient-year in patients treated with placebo. Serious infections were more common in Crohn's disease patients than ulcerative colitis patients, and anal abscesses were the most frequently reported serious adverse reaction in Crohn's disease patients. Over 48 months, there was no increase in the rate of serious infections.

In controlled- and open-label long-term extension trials in adults treated with ENTYVIO, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

In UC Trials I and II and CD Trials I and III, sepsis, including bacterial sepsis and septic shock, was reported in four of 1434 (0.3%) patients treated with ENTYVIO and in two of 297 patients treated with placebo (0.7%). During these trials, two Crohn's disease patients treated with ENTYVIO died due to reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open label long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported. The rate of sepsis in patients with ulcerative colitis or Crohn's disease receiving ENTYVIO was two per 1000 patient-years.

In clinical trials, all patients were screened for tuberculosis. One case of latent, pulmonary tuberculosis was diagnosed during the controlled trials with ENTYVIO. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the United States, and none of the patients had extrapulmonary manifestations.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO *[see Warnings and Precautions (5.4)]*. In UC Trials I and II and CD Trials I and III, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five ENTYVIO doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with ENTYVIO

and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

Malignancies

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1434 (0.4%) patients treated with ENTYVIO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary neuroendocrine carcinoma, renal cancer and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

Live and Oral Vaccines

There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO.

In a placebo-controlled study of healthy volunteers, 61 subjects were given a single ENTYVIO 750 mg dose (2.5 times the recommended dose), and 62 subjects received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with ENTYVIO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to ENTYVIO did have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In UC Trials I and II and CD Trials I and III, in patients who received ENTYVIO, the frequency of antibodies detected in patients was 13% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose). During treatment, 56 of 1434 (4%) of patients treated with ENTYVIO had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 patients were persistently positive (at two or more study visits) for anti-vedolizumab antibody and 33 of 56 patients developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations *[see Clinical Pharmacology (12.3)]*. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, presence of vedolizumab, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENTYVIO with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Natalizumab

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab.

7.2 TNF Blockers

Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO with TNF blockers.

7.3 Live Vaccines

Live vaccines may be administered concurrently with ENTYVIO only if the benefits outweigh the risks *[see Warnings and Precautions (5.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTYVIO during pregnancy. Information about the registry can be obtained by calling 1-877-TAKEDA7 (1-877-825-3327).

Pregnancy Category B:

Risk Summary

There are no studies with ENTYVIO in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefits to the mother outweigh the risk to the unborn child.

Clinical Considerations

Any adverse pregnancy effect from ENTYVIO would likely be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

8.3 Nursing Mothers

It is unknown whether vedolizumab is present in human milk. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of ENTYVIO in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials of ENTYVIO did not include sufficient numbers of subjects aged 65 and over (46 Crohn's and ulcerative colitis patients aged 65 and over were treated with ENTYVIO during controlled Phase 3 trials) to determine whether they respond differently from younger subjects. However, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

ENTYVIO (vedolizumab), an integrin receptor antagonist, is a humanized IgG_1 monoclonal antibody produced in Chinese hamster ovary cells that binds to the human α4β7 integrin. ENTYVIO has an approximate molecular weight of 147 kilodaltons.

ENTYVIO is supplied as a sterile, white to off-white, preservative-free, lyophilized cake for intravenous infusion. After reconstitution with 4.8 mL Sterile Water for Injection, USP, the resulting pH is approximately 6.3.

Each single-use vial contains 300 mg vedolizumab, 23 mg L-histidine, 21.4 mg L-histidine monohydrochloride, 131.7 mg L-arginine hydrochloride, 500 mg sucrose and 3 mg polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vedolizumab is a humanized monoclonal antibody that specifically binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. Vedolizumab does not bind to or inhibit function of the α4β1 and αEβ7 integrins and does not antagonize the interaction of α4 integrins with vascular cell adhesion molecule-1 (VCAM-1).

The α4β7 integrin is expressed on the surface of a discrete subset of memory T-lymphocytes that preferentially migrate into the gastrointestinal tract. MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T-lymphocytes to gut lymph tissue. The interaction of the α4β7 integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of ulcerative colitis and Crohn's disease.

12.2 Pharmacodynamics

In clinical trials with ENTYVIO at doses ranging from 0.2 to 10 mg/kg (which includes doses outside of the recommended dose), saturation of α4β7 receptors on subsets of circulating lymphocytes involved in gut-immune surveillance was observed.

In clinical trials with ENTYVIO at doses ranging from 0.2 to 10 mg/kg and 180 to 750 mg (which include doses outside of the recommended dose) in healthy subjects and in patients with ulcerative colitis or Crohn's disease, vedolizumab did not elevate neutrophils, basophils, eosinophils, B-helper and cytotoxic T-lymphocytes, total memory helper T-lymphocytes, monocytes or natural killer cells.

A reduction in gastrointestinal inflammation was observed in rectal biopsy specimens from Phase 2 ulcerative colitis patients exposed to ENTYVIO for four or six weeks compared to placebo control as assessed by histopathology.

In a study of 14 healthy subjects, ENTYVIO did not affect the CD4+ lymphocyte cell counts, CD8+ lymphocyte cell counts, or the CD4+:CD8+ ratios in the CSF *[see Clinical Pharmacology (12.3)]*.

12.3 Pharmacokinetics

Similar pharmacokinetics were observed in ulcerative colitis and Crohn's disease patients administered 300 mg ENTYVIO as a 30 minute intravenous infusion on Weeks 0 and 2, followed by 300 mg ENTYVIO every eight weeks starting from Week 6 *(Table 2).*

Table 2. Mean ± SD Vedolizumab Concentrations in Patients* with Ulcerative Colitis and Crohn's Disease

Patient Population	**Weeks 0 to 6**	**Weeks 6 to 52** ENTYVIO Every 8 Weeks
	Trough Serum Concentration at Week 6 (mcg/mL)	Trough Serum Concentration at Week 46† (mcg/mL)
Ulcerative Colitis	26.3 ± 12.9 (N=210)	11.2 ± 7.2 (N=77)
Crohn's Disease	27.4 ± 19.2 (N=198)	13.0 ± 9.1 (N=72)

*Data from patients in UC Trials I and II and CD Trials I and III with pharmacokinetic data available; data from patients with anti-vedolizumab antibody were excluded.
†Steady-state trough serum concentration.

The presence of persistent anti-vedolizumab antibody was observed to substantially reduce serum concentrations of vedolizumab, either to undetectable or negligible levels at Weeks 6 and 52 (n=8).

Vedolizumab clearance depends on both linear and nonlinear pathways; the nonlinear clearance decreases with increasing concentrations. Population pharmacokinetic analyses indicated that the linear clearance was approximately 0.157 L/day, the serum half-life was approximately 25 days at 300 mg dosage, and the distribution volume was approximately 5 L.

Vedolizumab was not detected in the cerebrospinal fluid (CSF) of 14 healthy subjects at five weeks after a single intravenous administration of 450 mg ENTYVIO (1.5 times the recommended dosage).

Special Populations

Population pharmacokinetic analysis showed that the severity of disease state, body weight, prior treatment with TNF blocker therapy, age (18 to 78 years), serum albumin, co-administered immunomodulators (including azathioprine, 6-mercaptopurine, methotrexate), and co-administered aminosalicylates did not have a clinically meaningful effect on the pharmacokinetics of ENTYVIO.

Pharmacokinetics of vedolizumab in patients with renal or hepatic insufficiency have not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of vedolizumab. Studies to evaluate the possible impairment of fertility or mutagenic potential of vedolizumab have not been performed.

14 CLINICAL STUDIES

14.1 Clinical Studies in Ulcerative Colitis

The safety and efficacy of ENTYVIO were evaluated in two randomized, double-blind, placebo-controlled trials (UC Trials I and II) in adult patients with moderately to severely active ulcerative colitis (UC) defined as Mayo score of six to 12 with endoscopy subscore of two or three. The Mayo score ranges from zero to 12 and has four subscales that are each scored from zero (normal) to three (most severe): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment. An endoscopy subscore of two is defined by marked erythema, lack of vascular pattern, friability, and erosions; an endoscopy subscore of three is defined by spontaneous bleeding and ulceration.

Enrolled patients in the United States (US) had over the previous five-year period an inadequate response or intolerance to immunomodulator therapy (i.e., azathioprine or 6-mercaptopurine) and/or an inadequate response, loss of response, or intolerance to a TNF blocker. Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous five-year period the patients were corticosteroid dependent (i.e., unable to successfully taper corticosteroids without a return of the symptoms of UC) or had an inadequate response or intolerance to corticosteroids.

Patients that had received natalizumab ever in the past, and patients that had received a TNF blocker in the past 60 days were excluded from enrollment. Concomitant use of natalizumab or a TNF blocker was not allowed.

UC Trial I

In UC Trial I, 374 patients were randomized in a double-blind fashion (3:2) to receive ENTYVIO 300 mg or placebo by intravenous infusion at Week 0 and Week 2. Efficacy assessments were at Week 6. Concomitant stable dosages of aminosalicylates, corticosteroids (prednisone dosage ≤30 mg/day or equivalent), and immunomodulators (azathioprine or 6-mercaptopurine) were permitted through Week 6.

At baseline, patients received corticosteroids (54%), immunomodulators (azathioprine or 6-mercaptopurine) (30%), and/or aminosalicylates (74%). Thirty-nine percent of patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. Eighteen percent of patients had an inadequate response, inability to taper or intolerance to prior corticosteroid treatment only (i.e., had not received prior immunomodulators or TNF blockers). The median baseline Mayo score was nine in the ENTYVIO group and eight in the placebo group.

In UC Trial I, a greater percentage of patients treated with ENTYVIO compared to patients treated with placebo achieved clinical response at Week 6 (defined in *Table 3*). A greater percentage of patients treated with ENTYVIO compared to patients treated with placebo also achieved clinical remission at Week 6 (defined in *Table 3*). In addition, a greater percentage of patients treated with ENTYVIO had improvement of endoscopic appearance of the mucosa at Week 6 (defined in *Table 3*).

Table 3. Proportion of Patients Meeting Efficacy Endpoints at Week 6 (UC Trial I)

Endpoint	Placebo N=149	ENTYVIO N=225	p-value	Treatment Difference and 95% CI
Clinical response* at Week 6	26%	47%	<0.001	22% (12%, 32%)
Clinical remission† at Week 6	5%	17%	0.001	12% (5%, 18%)
Improvement of endoscopic appearance of the mucosa‡ at Week 6	25%	41%	0.001	16% (6%, 26%)

*Clinical response: reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

†Clinical remission: complete Mayo score of ≤2 points and no individual subscore >1 point.

‡Improvement of endoscopic appearance of the mucosa: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

UC Trial II

In order to be randomized to treatment in UC Trial II, patients had to have received ENTYVIO and be in clinical response at Week 6. Patients could have come from either UC Trial I or from a group who received ENTYVIO open-label.

In UC Trial II, 373 patients were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: ENTYVIO 300 mg every eight weeks, ENTYVIO 300 mg every four weeks or placebo every four weeks. Efficacy assessments were at Week 52. Concomitant aminosalicylates and corticosteroids were permitted through Week 52. Concomitant immunomodulators (azathioprine or 6-mercaptopurine) were permitted outside the US but were not permitted beyond Week 6 in the US.

At Week 6, patients were receiving corticosteroids (61%), immunomodulators (azathioprine or 6-mercaptopurine) (32%) and aminosalicylates (75%). Thirty-two percent of patients had an inadequate response, loss of response or intolerance to a TNF blocker therapy. At Week 6, the median Mayo score was eight in the ENTYVIO every eight week group, the ENTYVIO every four week group, and the placebo group. Patients who had achieved clinical response at Week 6 and were receiving corticosteroids were required to begin a corticosteroid-tapering regimen at Week 6.

In UC Trial II, a greater percentage of patients in groups treated with ENTYVIO as compared to placebo achieved clinical remission at Week 52, and maintained clinical response (clinical response at both Weeks 6 and 52) *(Table 4)*. In addition, a greater percentage of patients in groups treated with ENTYVIO as compared to placebo were in clinical remission at both Weeks 6 and 52, and had improvement of endoscopic appearance of the mucosa at Week 52 *(Table 4)*. In the subgroup of patients who achieved clinical response at Week 6 and were receiving corticosteroid medication at baseline, a greater proportion of patients in groups treated with ENTYVIO as compared to placebo discontinued corticosteroids and were in clinical remission at Week 52 *(Table 4)*.

The ENTYVIO every four week dosing regimen did not demonstrate additional clinical benefit over the every eight dosing week regimen. The every four week dosing regimen is not the recommended dosing regimen *[see Dosage and Administration (2.3)]*.

Table 4. Proportion of Patients Meeting Efficacy Endpoints at Week 52[*] (UC Trial II)

Endpoint	Placebo[†] N=126	ENTYVIO Every 8 Weeks N=122	p-value	Treatment Difference and 95% CI
Clinical remission at Week 52	16%	42%	<0.001	26% (15%, 37%)
Clinical response at both Weeks 6 and 52	24%	57%	<0.001	33% (21%, 45%)
Improvement of endoscopic appearance of the mucosa[‡] at Week 52	20%	52%	<0.001	32% (20%, 44%)
Clinical remission at both Weeks 6 and 52	9%	21%	0.008	12% (3%, 21%)
Corticosteroid-free clinical remission[§]	14%[§]	31%[§]	0.012	18% (4%, 31%)

[*]Patients must have achieved clinical response at Week 6 to continue into UC Trial II. This group includes patients that were not in clinical remission at Week 6.

[†]The placebo group includes those patients who received ENTYVIO at Week 0 and Week 2 and were randomized to receive placebo from Week 6 through Week 52.

[‡]Improvement of endoscopic appearance of the mucosa: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability) at Week 52.

[§]Corticosteroid-free clinical remission: Assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response at Week 6 (n=72 for placebo and n=70 for ENTYVIO every eight weeks). Corticosteroid-free clinical remission was defined as the proportion of patients in this subgroup that discontinued corticosteroids by Week 52 and were in clinical remission at Week 52.

14.2 Clinical Studies in Crohn's Disease

The safety and efficacy of ENTYVIO were evaluated in three randomized, double-blind, placebo-controlled clinical trials (CD Trials I, II, and III) in adult patients with moderately to severely active Crohn's disease (CD) (Crohn's Disease Activity Index [CDAI] score of 220 to 450).[1]

Enrolled patients in the United States (US) had over the previous five-year period an inadequate response or intolerance to immunomodulator therapy (i.e., azathioprine, 6-mercaptopurine, or methotrexate) and/or an inadequate response, loss of response, or intolerance to one or more TNF blockers. Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous five-year period the patients were corticosteroid dependent (i.e., unable to successfully taper corticosteroids without a return of the symptoms of CD) or had an inadequate response or intolerance to corticosteroids.

Patients that had received natalizumab ever in the past, and patients that had received a TNF blocker in the past 30 to 60 days were excluded from enrollment. Concomitant use of natalizumab or a TNF blocker was not allowed.

CD Trial I

In CD Trial I, 368 patients were randomized in a double-blind fashion (3:2) to receive ENTYVIO 300 mg or placebo by intravenous infusion at Week 0 and Week 2. Efficacy assessments were at Week 6. Concomitant stable dosages of aminosalicylates, corticosteroids

(prednisone dosage ≤30 mg/day or equivalent), and immunomodulators (azathioprine, 6-mercaptopurine or methotrexate) were permitted through Week 6.

At baseline, patients were receiving corticosteroids (49%), immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) (35%), and/or aminosalicylates (46%). Forty-eight percent of the patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. Seventeen percent of patients had inadequate response, inability to taper, or intolerance to prior corticosteroid treatment only (i.e., had not received prior immunomodulators or TNF blockers). The median baseline CDAI score was 324 in the ENTYVIO group and 319 in the placebo group.

In CD Trial I, a statistically significantly higher percentage of patients treated with ENTYVIO achieved clinical remission (defined as CDAI ≤150) as compared to placebo at Week 6 *(Table 5)*. The difference in the percentage of patients who demonstrated clinical response (defined as a ≥100-point decrease in CDAI score from baseline), was however, not statistically significant at Week 6.

CD Trial II

Compared to CD Trial I, CD Trial II enrolled a higher number of patients who had over the previous five-year period had an inadequate response, loss of response, or intolerance to one or more TNF blockers (76%); this was the primary analysis population. In CD Trial II, 416 patients were randomized in a double-blind fashion (1:1) to receive either ENTYVIO 300 mg or placebo at Weeks 0, 2 and 6. Efficacy assessments were at Weeks 6 and 10. Concomitant aminosalicylates, corticosteroids, and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted through Week 10.

At baseline, patients were receiving corticosteroids (54%), immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) (34%), and aminosalicylates (31%). The median baseline CDAI score was 317 in the ENTYVIO group and 301 in the placebo group.

For the primary endpoint (clinical remission at Week 6), treatment with ENTYVIO did not result in statistically significant improvement over placebo *(Table 5)*. Secondary endpoints including assessments at Week 10 were not tested because the primary endpoint was not statistically significant.

Table 5. Proportion of Patients in Clinical Remission at Week 6 (CD Trials I and II)

	Placebo	**ENTYVIO**	**p-value**	**Treatment Difference and 95% CI**
CD Trial I: Clinical Remission* at Week 6	7% (10/148)	15% (32/220)	0.041‡	8% (1%, 14%)
CD Trial II†: Clinical Remission* at Week 6	12% (19/157)	15% (24/158)	NS§	3% (-5%, 11%)

*Clinical Remission: CDAI ≤150

†The primary analysis population for CD Trial II was patients that had an inadequate response, loss of response, or intolerance to one or more TNF blockers (76% of the overall population)

‡Adjusted p-value for multiple comparisons of two primary endpoints

§NS: Not significant (Secondary endpoints including assessments at Week 10 were not tested because the CD Trial II primary endpoint was not statistically significant)

CD Trial III

In order to be randomized to treatment in CD Trial III, patients had to have received ENTYVIO and be in clinical response (defined as a ≥70-point decrease in CDAI score from baseline) at Week 6. Patients could have come from either CD Trial I or from a group who received ENTYVIO open-label.

In CD Trial III, 461 patients were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: ENTYVIO 300 mg every eight weeks, ENTYVIO 300 mg every four weeks or placebo every four weeks. Efficacy assessments were at Week 52. Concomitant aminosalicylates and corticosteroids were permitted through Week 52. Concomitant immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted outside the US but were not permitted beyond Week 6 in the US.

At Week 6, patients were receiving corticosteroids (59%), immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) (31%), and aminosalicylates (41%). Fifty-one percent of patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. At Week 6, the median CDAI score was 322 in the ENTYVIO every eight week group, 316 in the ENTYVIO every four week group, and 315 in the placebo group. Patients who had achieved clinical response (≥70 decrease in CDAI score from baseline) at Week 6 and were receiving corticosteroids were required to begin a corticosteroid-tapering regimen at Week 6.

In CD Trial III a greater percentage of patients in groups treated with ENTYVIO as compared to placebo were in clinical remission (defined as CDAI score ≤150) at Week 52. A greater percentage of patients in groups treated with ENTYVIO as compared to placebo had a clinical response (defined as ≥100 decrease in CDAI score from baseline) at Week 52 *(Table 6)*. In the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response at Week 6 (defined as ≥70 decrease in CDAI score from baseline), a greater proportion of patients in groups treated with ENTYVIO as compared to placebo discontinued corticosteroids by Week 52 and were in clinical remission at Week 52 *(Table 6)*.

The ENTYVIO every four week dosing regimen did not demonstrate additional clinical benefit over the every eight dosing week regimen. The every four week dosing regimen is not the recommended dosing regimen *[see Dosage and Administration (2.3)]*.

Table 6. Proportion of Patients Meeting Efficacy Endpoints at Week 52* (CD Trial III)

	Placebo[†] N=153	**ENTYVIO Every 8 Weeks** N=154	**p-value**	**Treatment Difference and 95% CI**
Clinical remission[‡] at Week 52	22%	39%	0.001	17% (7%, 28%)
Clinical response[§] at Week 52	30%	44%	0.013	13% (3%, 24%)
Corticosteroid-free clinical remission[#]	16%[#]	32%[#]	0.015	16% (3%, 29%)

*This group includes patients that were not in clinical remission at Week 6. Patients must have achieved clinical response (defined as ≥70 decrease in CDAI from baseline) at Week 6 to continue into CD Trial III.

[†]The placebo group includes those patients who received ENTYVIO at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52

[‡]Clinical remission: CDAI ≤150

[§]Clinical response: ≥100 decrease in CDAI from baseline

[#]Corticosteroid-free clinical remission: Assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response (defined as ≥70 decrease in CDAI from baseline) at Week 6 (n=82 for placebo and n=82 for ENTYVIO every eight weeks). Corticosteroid-free clinical remission was defined as the proportion of patients in this subgroup that discontinued corticosteroids by Week 52 and were in clinical remission at Week 52.

15 REFERENCES

1. Best WR, Becktel JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70(3): 439-444

16 HOW SUPPLIED/STORAGE AND HANDLING

ENTYVIO (vedolizumab) is supplied in sterile 20 mL single-use glass vials, containing 300 mg of vedolizumab as a white to off-white cake.

NDC 64764-300-20 300 mg single-dose vial in individual carton

Refrigerate unopened vials at 2° to 8°C (36º to 46ºF). Retain in original package to protect from light.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Hypersensitivity Reactions

Instruct patients to report immediately if they experience symptoms consistent with a hypersensitivity reaction during or following an infusion of ENTYVIO *[see Warnings and Precautions (5.1)]*.

Infections

Inform patients that they may be more likely to develop infections when taking ENTYVIO. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection *[see Warnings and Precautions (5.2)]*.

Progressive Multifocal Leukoencephalopathy

Inform patients that progressive multifocal leukoencephalopathy (PML) has occurred in patients who received a different integrin receptor antagonist product. Instruct patients to report if they experience any new onset or worsening of neurological signs and symptoms immediately, as these could be indicative of PML *[see Warnings and Precautions (5.3)].*

Liver Injury

Inform patients that elevated transaminase levels with or without elevated bilirubin has occurred in patients who received ENTYVIO. Instruct patients to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice *[see Warnings and Precautions (5.4)]*.

Medication Guide

ENTYVIO (en ti' vee oh)
(vedolizumab)

What is the most important information I should know about ENTYVIO?

ENTYVIO may cause serious side effects, including:

- **Infusion and serious allergic reactions**. These reactions can happen while you are receiving ENTYVIO or several hours after treatment. You may need treatment if you have an allergic reaction. Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an infusion of ENTYVIO: rash, itching, swelling of your lips, tongue throat or face, shortness of breath or trouble breathing, wheezing, dizziness, feeling hot, or palpitations (feel like your heart is racing).
- **Infections.** ENTYVIO may increase your risk of getting a serious infection. Before receiving ENTYVIO and during treatment with ENTYVIO, tell your healthcare provider if you think you have an infection or have symptoms of an infection such as fever, chills, muscle aches, cough, shortness of breath, runny nose, sore throat, red or painful skin or sores on your body, tiredness, or pain during urination.
- **Progressive Multifocal Leukoencephalopathy (PML)**. Although it has not been reported with ENTYVIO, it may be possible for a person to get progressive multifocal leukoencephalopathy (PML) (a rare, serious brain infection caused by a virus). People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML. Tell your healthcare provider right away if you have any of the following symptoms: confusion or problems thinking, loss of balance, change in the way you walk or talk, decreased strength or weakness on one side of the body, blurred vision, or loss of vision.
- **Liver Problems**. Liver problems can happen in people who receive ENTYVIO. Tell your healthcare provider right away if you have any of the following symptoms: tiredness, loss of appetite, pain on the right side of your stomach (abdomen), dark urine, or yellowing of the skin and eyes (jaundice).

See **"What are the possible side effects of ENTYVIO?"** for more information about side effects.

What is ENTYVIO?

ENTYVIO is a prescription medicine used in adults:

- **with moderate to severe active ulcerative colitis (UC) when certain other UC medicines have not worked well enough or cannot be tolerated:**
  - to begin helping some of your symptoms
  - in people who respond to ENTYVIO, to help get UC under control (induce remission) and keep UC under control (maintain remission)
  - for people who respond to ENTYVIO, you may be able to reduce or stop the use of corticosteroid medicines
  - to improve the way the lining of your large intestine looks to your healthcare provider during colonoscopy

- **with moderate to severe active Crohn's disease when certain other Crohn's disease medicines have not worked well enough or cannot be tolerated:**
    - to begin helping some of your symptoms
    - in people who respond to ENTYVIO, to help get Crohn's disease under control (achieve remission)
    - for people who respond to ENTYVIO, you may be able to reduce or stop the use of corticosteroid medicines

It is not known if ENTYVIO is safe and effective in children under 18 years of age.

Who should not receive ENTYVIO?

Do not receive ENTYVIO if you have had an allergic reaction to ENTYVIO or any of the ingredients in ENTYVIO. See the end of this Medication Guide for a complete list of ingredients in ENTYVIO.

Before receiving ENTYVIO, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection, think you may have an infection or have infections that keep coming back **(see "What is the most important information I should know about ENTYVIO?")**.
- have liver problems
- have tuberculosis (TB) or have been in close contact with someone with TB.
- have recently received or are scheduled to receive a vaccine. Talk to your healthcare provider about bringing your vaccines up-to-date before starting treatment with ENTYVIO.
- are pregnant or plan to become pregnant. It is not known if ENTYVIO will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while receiving ENTYVIO.
- are breastfeeding or plan to breastfeed. It is not known if ENTYVIO passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Especially tell your healthcare provider if you take or have recently taken Tysabri (natalizumab), a Tumor Necrosis Factor (TNF) blocker medicine, a medicine that weakens your immune system (immunosuppressant), or corticosteroid medicine.

How will I receive ENTYVIO?

- ENTYVIO is given through a needle placed in a vein (intravenous infusion) in your arm.
- ENTYVIO is given to you over a period of about 30 minutes.
- Your healthcare provider will monitor you during and after the ENTYVIO infusion for side effects to see if you have a reaction to the treatment.

What are the possible side effects of ENTYVIO?

ENTYVIO may cause serious side effects, See **"What is the most important information I should know about ENTYVIO?"**

The most common side effects of ENTYVIO include: common cold, headache, joint pain, nausea, fever, infections of the nose and throat, tiredness, cough, bronchitis, flu, back pain, rash, itching, sinus infection, throat pain, and pain in extremities.

These are not all of the possible side effects of ENTYVIO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about ENTYVIO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about ENTYVIO that is written for health professionals. Do not use ENTYVIO for a condition for which it was not prescribed.

What are the ingredients in ENTYVIO?

Active ingredient: vedolizumab

Inactive ingredients: L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose and polysorbate 80

Distributed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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For more information, go to www.ENTYVIO.com or call 1-877-825-3327

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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