(No. 3799)
NEW

HUMIRA®
(adalimumab)

Rx only
Tear at Perforation to Dispense Patient Information

WARNING

RISK OF INFECTIONS

Cases of tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) have been observed in patients receiving HUMIRA.

Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA.

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:κ constant regions. HUMIRA 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 in single-use, 1 mL pre-filled glass syringes as a sterile, preservative-free solution for subcutaneous administration. The solution of HUMIRA is clear and colorless, with a pH of about 5.2. Each syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH.

CLINICAL PHARMACOLOGY

General

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 rheumatoid arthritis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of rheumatoid arthritis.

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).

Pharmacodynamics

After treatment with HUMIRA, a rapid 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. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

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 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- 96% of those in serum.

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. The 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.

Population pharmacokinetic analyses 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 patients receiving doses lower than the recommended dose and in 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.

HUMIRA has not been studied in children.

Drug Interactions

MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively.

CLINICAL STUDIES

The efficacy and safety of HUMIRA were assessed in four randomized, double-blind studies in patients ≥ age 18 with active rheumatoid arthritis 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 MTX (12.5 to 25 mg, Studies I and III) or as monotherapy (Study II) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV).

Study 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 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 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 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 104 weeks.

Study 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.

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies II and III are shown in Table 1.

Table 1: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

	Study II Monotherapy (26 weeks)			Study III Methotrexate Combination (24 and 52 weeks)	
Response	Placebo N=110	HUMIRA 40 mg every other week N=113	HUMIRA 40 mg weekly N=103	Placebo/MTX N=200	HUMIRA/MTX 40 mg every other week 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 I were similar to Study III; patients receiving HUMIRA 40 mg every other week in Study 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 II and III are shown in Table 2. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study 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.

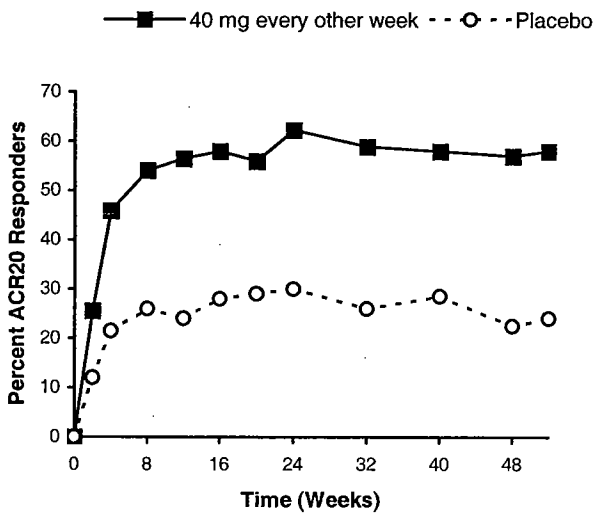
Table 2: Components of ACR Response in Studies II and III

Parameter (median)	Study II				Study III			
	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[2]; 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 III is shown in Figure 1.
In Study III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52weeks. The time course of ACR 20 response for Study I and Study II were similar.

Figure 1: Study III ACR 20 Responses over 52 Weeks



In Study 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.

Radiographic Response

In Study 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 3. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 3: Radiographic Mean Changes Over 12 Months in Study 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 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.

Physical Function Response

In all four studies, 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 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. Eighty-two percent of HUMIRA-treated patients who achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study maintained that improvement through week 104 of open-label treatment. Improvement in SF-36 was also maintained through week 104.

INDICATIONS AND USAGE

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. HUMIRA can be used alone or in combination with MTX or other DMARDs.

CONTRAINDICATIONS

HUMIRA should not be administered to patients with known hypersensitivity to HUMIRA or any of its components.

WARNINGS

SERIOUS INFECTIONS

SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF BLOCKING AGENTS INCLUDING HUMIRA. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS. TUBERCULOSIS AND INVASIVE OPPORTUNISTIC FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF BLOCKING AGENTS INCLUDING HUMIRA.

TREATMENT WITH HUMIRA SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH HUMIRA SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF HUMIRA SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF HUMIRA IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR UNDERLYING CONDITIONS WHICH MAY PREDISPOSE THEM TO INFECTIONS, OR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TUBERCULOSIS AND HISTOPLASMOSIS ARE ENDEMIC (see PRECAUTIONS - Tuberculosis and ADVERSE REACTIONS - Infections). THE BENEFITS AND RISKS OF HUMIRA TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF HUMIRA THERAPY.

Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents. Therefore, the combination of HUMIRA and anakinra is not recommended (see PRECAUTIONS, Drug Interactions).

Neurologic Events

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Malignancies

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with moderately to severely active rheumatoid arthritis, 2 lymphomas were observed among 1380 HUMIRA-treated patients versus 0 among 690 control patients (mean duration of controlled treatment approximately 7 months). In the controlled and open-label portions of these clinical trials of HUMIRA in rheumatoid arthritis patients, 10 lymphomas were observed in 2468 patients over 4870 patient-years of therapy. This is approximately 5-fold higher than expected in the general population. Rates in clinical trials for HUMIRA cannot be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population.. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma. The potential role of TNF-blocking therapy in the development of malignancies is not known. (see **ADVERSE REACTIONS: Malignancies**).[4,5]

Hypersensitivity Reactions

In postmarketing experience, anaphylaxis has been reported rarely following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

Hematologic Events

Rare reports of pancytopenia including aplastic anemia have been reported with TNFα-blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA (see

ADVERSE REACTIONS, Other Adverse Reactions). The causal relationship of these reports to HUMIRA remains unclear. 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, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

PRECAUTIONS

Information to Patients

The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA (see **HUMIRA, PATIENT INFORMATION LEAFLET**). A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

Tuberculosis

As observed with other TNF blocking agents, tuberculosis associated with the administration of HUMIRA in clinical trials has been reported (see **WARNINGS**). While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of HUMIRA that were higher than the recommended dose. All patients recovered after standard antimicrobial therapy. No deaths due to tuberculosis occurred during the clinical trials.

Before initiation of therapy with HUMIRA, patients should be evaluated for active or latent tuberculosis infection with a tuberculin skin test. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Centers for Disease Control and Prevention guidelines[6] should be instituted. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur.

Patients with 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 events was observed. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Immunosuppression

The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with HUMIRA on the development and course of malignancies, as well as active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections and Malignancies**). The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

Immunizations

No data are available on the effects of vaccination in patients receiving HUMIRA. Live vaccines should not be given concurrently with HUMIRA. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

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, treatment should be discontinued (see **ADVERSE REACTIONS, Autoantibodies**).

Drug Interactions

Methotrexate

HUMIRA has been studied in rheumatoid arthritis patients taking concomitant MTX (see **CLINICAL PHARMACOLOGY: Drug Interactions**). The data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including HUMIRA, may also result in similar toxicities (see **WARNINGS, SERIOUS INFECTIONS**).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

Pregnancy

Pregnancy Category B - An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneous with MTX every week or 373 times human AUC when given 40 mg subcutaneous without MTX) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.
Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972

Nursing Mothers

It is not known whether adalimumab 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 serious adverse reactions in nursing infants from HUMIRA, 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.

Pediatric Use

Safety and effectiveness of HUMIRA in pediatric patients have not been established.

Geriatric Use

A total of 519 patients 65 years of age and older, including 107 patients 75 years and older, received HUMIRA in clinical studies. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

ADVERSE REACTIONS

General

The most serious adverse reactions were (see **WARNINGS**):

- Serious Infections
- Neurologic Events
- Malignancies

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 events during the double-blind, placebo-controlled portion of Studies I, II, III and IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse events leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

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

Infections

In placebo-controlled trials, the rate of infection was 1 per patient-year in the HUMIRA-treated patients and 0.9 per patient-year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient-year in HUMIRA-treated patients and 0.02 per patient-year in placebo-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis (see **WARNINGS**).

Thirteen cases of tuberculosis, including miliary, lymphatic, peritoneal, and pulmonary, were reported in clinical trials. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Six cases of invasive opportunistic infections caused by histoplasma, aspergillus, and nocardia were also reported in clinical trials (see **WARNINGS**).

Malignancies

Among 2468 rheumatoid arthritis patients with moderately to severely active disease treated with HUMIRA in clinical trials for a mean of 24 months (4870 patient-years of therapy), 10 lymphomas were observed for a rate of 0.21 cases per 100 patient-years. This is approximately 5-fold higher than expected in an age- and sex-matched general population based on the Surveillance, Epidemiology, and End Results Database.[7] Rates in clinical trials for HUMIRA can not be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. (see **WARNINGS: Malignancies**). An increased rate of lymphoma has been reported in the rheumatoid arthritis patient population. [5,6] Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma. The potential role of TNF-blocking therapy in the development of malignancies is not known. Thirty-eight malignancies, other than lymphoma, were observed. Of these, the most common malignancies were breast, colon, prostate, and uterine, which were similar in type and number to what would be expected in the general population.[7]

Autoantibodies

In the 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. One patient out of 2334 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patient 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.

Immunogenicity

Patients in Studies I, II, and 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 rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events 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.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, 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 adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

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 I, II, III, and 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 4 summarizes events 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. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week. In Study III, the types and frequencies of adverse events in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 4: Adverse Events Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

Adverse Event (Preferred Term)	HUMIRA 40 mg subcutaneous Every Other Week (N=705) Percentage	Placebo (N=690) Percentage
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		
Injection site pain	12	12
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 events in European trials

** Does not include erythema and/or itching, hemorrhage, pain or swelling

Other Adverse Events

Other infrequent serious adverse events occurring at an incidence of less than 5% in patients treated with HUMIRA were:

Body As A Whole: Fever, infection, pain in extremity, pelvic pain, sepsis, surgery, thorax pain, tuberculosis reactivated

Cardiovascular System: Arrhythmia, atrial fibrillation, cardiovascular disorder, chest pain,

congestive heart failure, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, vascular disorder

Collagen Disorder: Lupus erythematosus syndrome

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

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, granulocytopenia, leukopenia, lymphoma like reaction, pancytopenia, polycythemia (see **WARNINGS, Hematologic Events**).

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, carcinomas such as breast, gastrointestinal, skin, urogenital, and others; lymphoma and melanoma.

Nervous System: Confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor

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

Skin And Appendages: Cellulitis, erysipelas, herpes zoster

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder, pyelonephritis

Adverse Reaction Information from Spontaneous Reports:

Adverse events have been reported during post-approval use of HUMIRA. 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 HUMIRA exposure

Hematologic Events: Thrombocytopenia (see **WARNINGS, Hematologic Events**).

Hypersensitivity reactions: Anaphylaxis (see **WARNINGS, Hypersensitivity Reactions**).

Skin reactions: cutaneous vasculitis.

OVERDOSAGE

The maximum tolerated dose of HUMIRA has not been established in humans. Multiple 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.

DOSAGE AND ADMINISTRATION

The recommended dose of HUMIRA for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection. MTX, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with HUMIRA. Some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

HUMIRA is intended for use under the guidance and supervision of a physician. Patients may self-inject HUMIRA if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

The solution in the syringe should be carefully inspected visually for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, the product should not be used. HUMIRA does not contain preservatives; therefore, unused portions of drug remaining from the syringe should be discarded. NOTE: The needle cover of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.

Patients using the pre-filled syringes should be instructed to inject the full amount in the syringe (0.8 mL), which provides 40 mg of HUMIRA, according to the directions provided in the Patient Information Leaflet.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red or hard (see **PATIENT INFORMATION LEAFLET**).

Instructions For Activating the Needle Stick Device: Cartons for institutional use contain a syringe and needle with a needle protection device (see **HOW SUPPLIED**). To activate the needle stick protection device after injection, hold the syringe in one hand and, with the other hand, slide the outer protective shield over the exposed needle until it locks into place.

Storage and Stability

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 2-8° C (36-46° F). DO NOT FREEZE. Protect the pre-filled syringe from exposure to light. Store in original carton until time of administration.

HOW SUPPLIED

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

Patient Use Syringe Carton

HUMIRA is dispensed 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 40 mg (0.8 mL) of HUMIRA. **The NDC number is 0074-3799-02.**

Institutional Use Syringe Carton

Each carton contains two alcohol preps and one dose tray. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge ½ inch needle (with a needle stick protection device) providing 40 mg (0.8 mL) of HUMIRA. **The NDC number is 0074-3799-01.**

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HUMIRA®
(adalimumab)
Patient Information

Read this leaflet carefully before you start taking HUMIRA **(hu-mare-ah)**. You should also read this leaflet each time you get your prescription refilled, in case something has changed. The information in this leaflet does not take the place of talking with your doctor before you start taking this medicine and at check ups. Talk to your doctor if you have any questions about your treatment with HUMIRA.

What is HUMIRA?
HUMIRA is a medicine that is used in people with moderate to severe rheumatoid arthritis (RA). RA is an inflammatory disease of the joints. People with RA are usually given other medicines for their disease before they are given HUMIRA. HUMIRA is for people with RA who have not responded well enough to these other medicines.

How does HUMIRA work?
HUMIRA is a medicine called a *TNF blocker*, that is a type of protein that blocks the action of a substance your body makes called TNF-alpha. TNF-alpha (tumor necrosis factor alpha) is made by your body's immune system. People with RA have too much of it in their bodies. The extra TNF-alpha in your body can attack normal healthy body tissues and cause inflammation especially in the tissues in your bones, cartilage, and joints. HUMIRA helps reduce the signs and symptoms of RA (such as pain and swollen joints), may help prevent further damage to your bones and joints and may help improve your ability to perform daily activities.
HUMIRA can block the damage that too much TNF-alpha can cause, and it can also lower your body's ability to fight infections. Taking HUMIRA can make you more prone to getting infections or make any infection you have worse.

Who should not take HUMIRA?
You should not take HUMIRA if you have an allergy to HUMIRA or to any of the ingredients (including sodium phosphate, sodium citrate, citric acid, mannitol, and polysorbate 80). The needle cover on the pre-filled syringe contains dry natural rubber. Tell your doctor if you have any allergies to rubber or latex.

Before you start taking HUMIRA you should tell your doctor if you have or have had any of the following:

- Any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from HUMIRA. If you are unsure, please ask your doctor.

- A history of infections that keep coming back or other conditions that might increase your risk of infections.

- If you have ever had tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis. If you develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor right away. Your doctor will need to examine you for TB and perform a skin test.

- If you experience any numbness or tingling or have ever had a disease that affects your nervous system like multiple sclerosis.

- If you are scheduled to have major surgery.

- If you are scheduled to be vaccinated for anything.

If you are not sure or have any questions about any of this information, ask your doctor.

What important information do I need to know about side effects with HUMIRA?
Any medicine can have side effects. Like all medicines that affect your immune system, HUMIRA can cause serious side effects. The possible serious side effects include:

Serious infections: There have been rare cases where patients taking HUMIRA or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria or fungi. Some patients have died when the bacteria that cause infections have spread throughout their body (sepsis).

Nervous system diseases: There have been rare cases of disorders that affect the nervous system of people taking HUMIRA or other TNF blockers. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling, problems with your vision, weakness in your legs and dizziness.

Malignancies: There have been very rare cases of certain kinds of cancer in patients taking HUMIRA or other TNF blockers. People with more serious RA that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you take HUMIRA or other TNF blockers, your risk may increase.

Lupus-like symptoms: Some patients have developed lupus-like symptoms that got better after their treatment was stopped. If you have chest pains that do not go away, shortness of breath, joint pain or a rash on your cheeks or arms that is sensitive to the sun, call your doctor right away. Your doctor may decide to stop your treatment.

Blood Problems: In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that doesn't go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

Heart Problems: You should tell your doctor if you have ever been treated for heart failure. If you have, your doctor may choose not to start you on HUMIRA, or may want to monitor you more closely. If you develop new or worsening problems like shortness of breath or swelling of your ankles or feet, you should call your doctor right away.

Allergic reactions: If you develop a severe rash, swollen face or difficulty breathing while taking HUMIRA, call your doctor right away. In rare cases, patients taking HUMIRA have had severe allergic reactions leading to difficulty breathing and low blood pressure, or shock. Allergic reactions can happen after your first dose or may not happen until after you have taken HUMIRA many times. If you develop a severe rash, swollen face or difficulty breathing while taking HUMIRA, call your doctor right away or seek emergency care immediately.

What are the other more common side effects with HUMIRA?

Many patients experience a reaction where the injection was given. These reactions are usually mild and include redness, rash, swelling, itching or bruising. Usually, the rash will go away within a few days. If the skin around the area where you injected HUMIRA still hurts or is swollen, try using a towel soaked with cold water on the injection site. If you have pain, redness or swelling around the injection site that doesn't go away within a few days or gets worse, call your doctor right away. Other side effects are upper respiratory infections (sinus infections), headache and nausea.

Can I take HUMIRA if I am pregnant or breast-feeding?

HUMIRA has not been studied in pregnant women or nursing mothers, so we don't know what the effects are on pregnant women or nursing babies. You should tell your health care provider if you are pregnant, become pregnant or are thinking about becoming pregnant. If you take this medication while you are pregnant, or if you become pregnant while taking HUMIRA you are encouraged to participate in a pregnancy registry to gather additional information about the use of HUMIRA during pregnancy by calling 1-877-311-8972.

Can I take HUMIRA if I am taking other medicines for my RA or other conditions?

Yes, you can take other medicines provided your doctor has prescribed them, or has told you it is ok to take them while you are taking HUMIRA. It is important that you tell your doctor about any other medicines you are taking for other conditions (for example, high blood pressure medicine) before you start taking HUMIRA.

You should also tell your doctor about any over-the-counter drugs, herbal medicines and vitamin and mineral supplements you are taking.

You should not take HUMIRA with other TNF blockers. If you have questions, ask your doctor.

How do I take HUMIRA?

You take HUMIRA by giving yourself an injection under the skin once every other week, or more frequently (every week) if your doctor tells you to. If you accidentally take more HUMIRA than you were told to take, you should call your doctor. Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or the HUMIRA Patient Resource Center at 1-800-4HUMIRA (448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection. Remember to take this medicine just as your doctor has told you and do not miss any doses.

What should I do if I miss a dose of HUMIRA?

If you forget to take HUMIRA when you are supposed to, inject the next dose right away. Then, take your next dose when your next scheduled dose is due. This will put you back on schedule.

Is one time better than another for taking HUMIRA?

Always follow your doctor's instructions about when and how often to take HUMIRA. To help you remember when to take HUMIRA, you can mark your calendar ahead of time with the stickers provided in the back of the patient information booklet. For other information and ideas you can enroll in a patient support program by calling the HUMIRA Patient Resource Center at 1-800-4HUMIRA (448-6472).

What do I need to do to prepare and give an injection of HUMIRA?

1) Setting up for an injection

- Find a clean flat working surface.
- Remove one dose tray containing a pre-filled syringe of HUMIRA from the refrigerator. Do not use a pre-filled syringe that is frozen or if it has been left in direct sunlight.

You will need the following items for each dose:

- A dose tray containing a pre-filled syringe of HUMIRA with a fixed needle
- 1 alcohol prep

If you do not have all of the pieces you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA comes in.

- Check and make sure the name HUMIRA appears on the dose tray and pre-filled syringe label.
- Check the expiration date on the dose tray label and pre-filled syringe to make sure the date has not passed. Do not use a pre-filled syringe if the date has passed.
- Make sure the liquid in the pre-filled syringe is clear and colorless. Do not use a pre-filled syringe if the liquid is cloudy or discolored or has flakes or particles in it.

- Have a puncture proof container nearby for disposing of used needles and syringes.

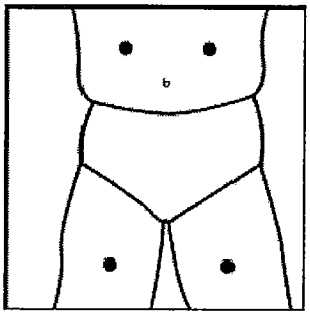
FOR YOUR PROTECTION, IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS.

2) Choosing and preparing an injection site

- Wash your hands thoroughly
- Choose a site on the front of your thighs or your abdomen. If you choose your abdomen, you should avoid the area 2 inches around your navel.

    - 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 areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.

    - You may find it helpful to keep notes on the location of previous injections.



- Wipe the site where HUMIRA is to be injected with an alcohol prep, using a circular motion. Do NOT touch this area again until you are ready to inject.

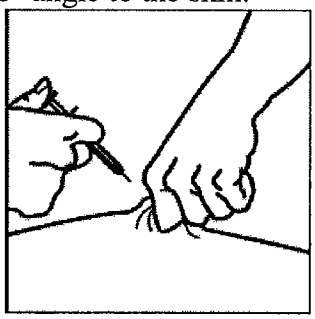
3) How to prepare your HUMIRA dose for injection with a Pre-filled Syringe

- Hold the syringe upright with the needle facing down Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line shown on the pre-filled syringe. 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.
- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.

- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is ok.

4) Injecting HUMIRA

- With your other hand, gently pinch the cleaned area of skin and hold it firmly. Hold the syringe like a pencil at about a 45° angle to the skin.



- With a quick, short, "dart-like" motion, push the needle into the skin.

- After the needle is in, let go of the skin. Pull back slightly on the plunger, if blood appears in the syringe it means that you have entered a blood vessel. Do not inject HUMIRA. Withdraw the needle and repeat the steps to choose and clean a new injection site. DO NOT use the same syringe; discard it in your puncture proof container. If no blood appears, slowly push the plunger all the way in until all of the HUMIRA is injected.

- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was inserted.

- Press a cotton ball over the injection site and hold it for 10 seconds. Do **NOT** rub the injection site. If you have slight bleeding, do not be alarmed.

- Dispose of the syringe immediately.

5) Disposing of syringes and needles

You should always check with your healthcare provider for instructions on how to properly dispose of used needles and syringes. You should follow any special state or local laws regarding the proper disposal of needles and syringes. **DO NOT throw the needle or syringe in the household trash or recycle.**

- Place the used needles and syringes in a container made specially for disposing of used syringes and needles (called a "Sharps" container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labeled *"Used Syringes"*. Do not use glass or clear plastic containers.
- Always keep the container out of the reach of children.

- When the container is about two-thirds full, tape the cap or lid down so it does not come off and dispose of it as instructed by your doctor, nurse or pharmacist. DO NOT THROW THE CONTAINER IN THE HOUSEHOLD TRASH OR RECYCLE.
- Used preps may be placed in the trash, unless otherwise instructed by your doctor, nurse or pharmacist. The dose tray and cover may be recycled.

HOW DO I STORE HUMIRA?

Store at 2°C – 8°C/36-46°F (in a refrigerator) in the original container until it is used. Protect from light. DO NOT FREEZE HUMIRA. Refrigerated HUMIRA remains stable until the expiration date printed on the pre-filled syringe. If you need to take it with you, such as when traveling, store it in a cool carrier with an ice pack and protect it from light.

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

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