

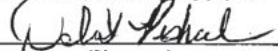
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20 November 2009

(Date of Deposit)

Deborah Pishock

(Name of person mailing paper)


(Signature)

20 November 2009

(Date of Signature)

RECEIVED
NOV 20 2009
PATENT EXTENSION
OPLA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 6,902,734

Issued:

June 7, 2005

Expiration Date:

July 27, 2022

Inventors: Jill Giles-Komar; David M. Knight; David Peritt; Bernard Scallon; David Shealy

Title: ANTI-IL-12 ANTIBODIES AND COMPOSITIONS THEREOF

Mail Stop Hatch-Waxman PTE

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740)

Pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Centocor Ortho Biotech Inc. ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for extension of U.S. Patent No. 6,902,734 (the '734 Patent). As permitted by 37 C.F.R. § 1.785(b) and MPEP § 2761, Applicant is concurrently filing a request for patent term extension of U.S. Patent No. 7,166,285 based upon the same regulatory review period.

In support of such Petition, Applicant provides the following information:

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Eric A. Dichter, represent that I am a registered practitioner appointed by the patent owner of record. A Power of Attorney, authorizing Eric A. Dichter to act on behalf of the Patent Owner is attached hereto as Exhibit 6.

B. RECORDAL OF ASSIGNMENT IN PTO

The application for the '734 Patent, U.S. Serial No. 09/920,262, filed August 1, 2001, claiming priority from U.S. Provisional Application No. 60/236,827, filed September 29, 2000, and U.S. Provisional Application No. 60/223,358, was filed August 7, 2000. An assignment of U.S. Serial No. 09/920,262 was recorded: Date: August 31, 2001 at Reel/Frame: 012151/0217 from the named inventors to Centocor, Inc. The successor entity to Centocor, Inc. is Centocor Ortho Biotech Inc. A merger document changing the entity owning U.S. Patent No. 6,902,734 from Centocor, Inc. to Centocor Ortho Biotech Inc. was recorded: Date: November 13, 2009 at Reel/Frame: 023510/0420.

II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

The United States Food and Drug Administration ("FDA") has approved Biologics License Application ("BLA") No. 125261/0 for STELARA™ (ustekinumab). The active ingredient of STELARA™ is ustekinumab. A copy of the FDA Approval Letter and the approved labeling is attached hereto as Exhibit 1.

The active ingredient in the approved product, ustekinumab, is comprised of 1,326 amino acids. The amino acid sequence for ustekinumab is as follows:

(A)

FW1	EVQLVQSGAEVKKPGESLKISCKGSGYSFT
CDR1	TYWLG
FW2	WVRQMPGKGLDWIG
CDR2	IMSPVDSIRYSPSFQG
FW3	QVTMSVDKSITTAYLQWNSLKASDTAMYCAR
CDR3	RRPGQGYFDF
FW4	WGQGTLLTVSS
CH1	SSTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
HINGE	EPKSCDKTHTCPPCPAPELLG
CH2	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAK
CH3	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK

(B)

FW1	DIQMTQSPSSLSASVGDRVTITC
CDR1	RASQGISSWLA
FW2	WYQQKPEKAPKSLIY
CDR2	AASSLQS
FW3	GVPSRFGSGSGTDFTLTISSLQPEDFATYYC
CDR3	QQYNIYPYT
FW4	FGQGTKLEIK
CK	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC

B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

Regulatory review for this product occurred under Section 351(a) of the Public Health Service Act (42 U.S.C. § 262(a)) (21 C.F.R. §§ 314 and 601) and Section 505(i) of the Federal Food Drug & Cosmetic Act ("FDC Act") 21 U.S.C. § 355(i) (21 C.F.R. § 312) (new drugs).

C. DATE OF APPROVAL (1.740(a)(3))

The FDA approved No. 125261/0 for STELARA™ for commercial marketing or use under Section 351(a) of the Public Health Service Act (42 U.S.C. § 262(a)) on September 25, 2009.

D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

STELARA™ (ustekinumab) is a human drug product, the sole active ingredient of which is ustekinumab. Ustekinumab has not been previously approved, alone or in combination, for commercial marketing or use under the Federal Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5))

This application is being submitted within the sixty-day time period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last date this application may be submitted is November 24, 2009.

F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of the Inventors: Jill Giles-Komar; David M. Knight; David Peritt; Bernard Scallon; David Shealy

Patent No. 6,902,734

Date of Issue: June 7, 2005

Date of Original Expiration: July 27, 2022 (including Patent Term Adjustment under 35 U.S.C. § 154(b))

A copy of the patent, including the entire specification (including claims) and drawings is attached as Exhibit 2.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statements is attached as Exhibit 3.

No terminal disclaimer or reexamination certificate has been filed or issued in the '734 patent.

G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The '734 patent claims the active ingredient and a composition of the approved product, which is ustekinumab. The claims directed to the approved product are claims 1-4. A complete claim chart that lists each applicable claim of the '734 patent and demonstrates the manner in which each applicable claim reads on the approved product is attached as Exhibit 4.

H. RELEVANT DATES AND INFORMATION (1.740(a)(10))

The '734 Patent claims a human drug.

The effective date of the investigational new drug (IND) application was December 28, 2000, and the IND No. is BB-IND 9590.

The biologics license application (BLA) was initially submitted on November 28, 2007 and was received by the FDA on November 29, 2007. The BLA Number is 125261/0.

The BLA was approved on September 25, 2009.

I. DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))

Attached as **Exhibit 5** is a "DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW" that provides a description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved Product and the significant dates applicable to such activities.

J. STATEMENT THAT PATENT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))

Attached as Exhibit 7 is a "STATEMENT THAT PATENT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED" that states that in the opinion of the applicant the '734 Patent is eligible for the extension and the length of extension claimed, including how the length of extension was determined.

K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Eric A. Dichter, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension being sought herein.

L. FEE (1.740(a)(14))

The Application fee due is \$1,120.00 (37 C.F.R. § 1.740(a)(14) and § 1.20(j)).

Authorization is hereby made to charge the amount of \$1,120.00 to Deposit Account No. 10-0750/CEN0248/EAD.

Please also charge any additional fees required by this paper or credit any overpayment to Deposit Account No. 10-0750.

M. CORRESPONDENCE (1.740(a)(15))

Please direct all inquiries and correspondence relating to this application to:

Philip Johnson, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

Attn: Eric A. Dichter

Phone: (610) 651-7491

Facsimile: (732) 524-2808

N. COPIES (1.740(a)(15)(b)) and MPEP 2753

Four additional copies of this application are attached, making a total of five copies being submitted.

Conclusion

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that U.S. Patent No. 6,902,734 is entitled to the requested 425 day extension of its term to September 25, 2023.

Prompt action on this application is respectfully requested.

Date: 20 November 2009

/Eric Dichter/

Reg. No.: 41,708

Tel. No.: 610-651-7491

Customer No.: 000027777

Eric A. Dichter, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
U.S.A.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125261/0

BLA APPROVAL
September 25, 2009

Centocor Ortho Biotech, Inc.
Attention: Kim Shields-Tuttle
Senior Director, Global Regulatory Affairs, Immunology
200 Great Valley Parkway
Malvern, PA 19355

Dear Ms. Shields-Tuttle:

Please refer to your biologics license application, dated November 28, 2007, received November 29, 2007, submitted under section 351 of the Public Health Service Act for StelaraTM (ustekinumab).

We acknowledge receipt of your submissions dated November 7 and 21 and December 8, 12, 16, and 18, 2008; January 9, March 5, 23, and 27, April 1, 10, and 27, May 1 and 13, June 25 and 26, July 24, August 5, 11, 12, 14, 17, 21 and 27, and September 11 and 23, 2009.

The January 9, 2009 submission constituted a complete response to our December 18, 2008 action letter.

We have approved your biologics license application for StelaraTM (ustekinumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, StelaraTM (ustekinumab) under your existing Department of Health and Human Services U.S. License No. 1821. StelaraTM (ustekinumab) is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Under this license, you are approved to manufacture StelaraTM (ustekinumab) drug substance at Centocor Biologics, LLC in St. Louis, Missouri. The final formulated product will be manufactured, filled, labeled, and packaged at Cilag AG, Schaffhausen, Switzerland. You may label your product with the proprietary name StelaraTM and will market it in 45 mg/0.5 mL and 90 mg/1 mL vials.

StelaraTM (ustekinumab) Pre-Filled Syringe, 45 mg/0.5 mL and 90 mg/1 mL is not approved and review will continue under STN BL 125261/1.

The dating period for StelaraTM (ustekinumab) drug product shall be 12 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. The dating period for bulk drug substance

shall be 36 months when stored at -40 °C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug product and drug substance under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Stelara™ (ustekinumab) 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.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of ustekinumab, or in the manufacturing facilities.

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.

We are deferring submission of your pediatric protocol until December 1, 2022 because pediatric studies should be delayed until additional adult safety and efficacy data have been collected. Pediatric studies are deferred pending analyses of a) safety data from adults in PHOENIX 1 (C0743T08), PHOENIX 2 (C0743T09), the PSOLAR registry, and the Nordic Database Initiative (discussed in items 2, 3, 8, and 9) and b) safety data in pediatric subjects exposed to Stelara™ (ustekinumab) *in utero* or postnatally (described in Items 4, 5, and 6). These safety analyses must establish that there are no safety issues that would preclude study of pediatric subjects. Pediatric studies should not be undertaken until there is agreement with the Agency on the design of such studies.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

1. Conduct studies to evaluate the safety and efficacy of ustekinumab in pediatric subjects with plaque psoriasis.

Pediatric Protocol Submission Date:

December 1, 2022

Submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment.**"

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

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 the known risk of serious infection; or to identify unexpected serious risks of malignancy, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic events, adverse pregnancy and fetal outcomes, adverse effects on immune system development, or altered metabolism of co-administered drugs.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies:

2. Enroll 4,000 Stelara™ (ustekinumab)-treated subjects into the Psoriasis Longitudinal Assessment and Registry, (PSOLAR) and follow for 8 years from the time of enrollment. Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events,

Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013, 2014
Interim Summary Report:	2015
Annual Reports:	2016, 2017, 2018, 2019
Study Completion Date:	December 1, 2019
Final Report Submission:	December 1, 2020

3. Provide data analyses from the Nordic Database Initiative regarding the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events with exposure to ustekinumab.

Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013, 2014
Interim Summary Report:	2015
Annual Reports:	2016, 2017, 2018, 2019
Study Completion Date:	December 15, 2019
Final Report Submission:	December 15, 2020

4. Establish a U.S.-based prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to Stelara™ (ustekinumab) during pregnancy to an unexposed control population. Outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life.

Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013
Study Completion Date:	July 15, 2013
Final Report Submission:	July 15, 2014

5. Provide data analyses from the Pregnancy Research Initiative (study C0168T71).

Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013, 2014
Interim Summary Report:	2015
Annual Reports:	2016, 2017, 2018, 2019, 2020
Study Completion Date:	December 15, 2020
Final Report Submission:	December 15, 2021

6. Conduct a lactation study in women who are breastfeeding while exposed to Stelara™ (ustekinumab). This study may be conducted in a subset of women enrolled in the U.S.-based pregnancy registry (discussed in PMR # 4) who choose to breastfeed their infants, and should assess for the presence of Stelara™ (ustekinumab) in breast milk and potential adverse effects in nursing infants.

Submit this information according to the following timetable:

Final Protocol Submission:	January 15, 2010
Annual Reports:	2011, 2012, 2013
Study Completion Date:	July 15, 2013
Final Report Submission:	July 15, 2014

7. Conduct an *in vitro* study to assess whether IL-12 and/or IL-23 modulate expression of major CYP enzymes (i.e., CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2D6). If, upon review, there is no marked modulation of any of the major CYP enzyme(s) observed, further exploration would not be necessary.

The timetable you submitted on August 17, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	February 2010
Study Completion Date:	July 2010
Final Report Submission:	December 2010

Finally, we have determined that only clinical trials (rather than an observational study) will be sufficient to assess the known risk of serious infection; or to identify unexpected serious risks of malignancy, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic events, or altered metabolism from co-administered drugs.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trials:

8. Complete the treatment and evaluation of subjects enrolled in the ongoing PHOENIX 1 (C0743T08) trial for a total of 5 years from initial enrollment unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through 5 years (even if treatment is not continued for this duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

The timetable you submitted on August 5, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	September 2005
Trial Completion Date:	May 2011
Final Report Submission:	January 2012

9. Complete the treatment and evaluation of subjects enrolled in the ongoing PHOENIX 2 (C0743T09) trial for a total of 5 years from initial enrollment unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through 5 years (even if treatment is not continued for this duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity

reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

The timetable you submitted on August 5, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	December 2005
Trial Completion Date:	October 2011
Final Report Submission:	June 2012

10. If the results of the *in vitro* study (discussed under PMR #7) are positive (i.e., if there is marked modulation of any of the major CYP enzyme(s)) conduct a clinical trial to determine the potential of ustekinumab to alter CYP substrate metabolism in psoriasis patients (e.g., using a cocktail of relevant CYP probe drugs).

The timetable you submitted on August 17, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	September 2011
Trial Completion Date:	December 2012
Final Report Submission:	September 2013

Submit the protocols to your IND, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Using the following designators to prominently label all submissions, including supplements, relating to these postmarketing study requirements 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
OF 21 CFR 601.70**

We also acknowledge your written commitments as described in your letter dated August 5, 14, and 17, 2009 as outlined below:

11. Provide information on maintenance of response with dosing intervals longer than every 12 weeks among relevant populations (e.g., subjects whose psoriasis is cleared as measured by PGA and PASI or who have minimal psoriasis). This information will be obtained from a study of at least 300 subjects treated with Stelara™ (ustekinumab) for a minimum of one year.

The study should not be undertaken until there is agreement with the Agency on the design of your study.

Concept Paper Submission:	March 2010
Draft Protocol Submission:	September 2010
Final Protocol Submission:	December 2010
Final Report Submission:	6 months after completion of study

12. Evaluate approaches to improve drug tolerance in the assay method for anti-drug antibodies (ADA). If a suitable method is developed, it will be applied to assess ADA in patient samples banked from the pivotal trials, if available, and on-going clinical trials. Alternatively, documentation will be submitted to the FDA demonstrating, with due diligence, that such an assay could not be feasibly developed.

Final Report Submission:	December 31, 2012
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13. Establish quantitative drug product release and stability specifications for the non-reduced cSDS assay when sufficient commercial experience with the assay has been gained. A proposed specification including justification based on supporting data will be submitted as a prior approval supplement.

Final Report Submission:	September 2011
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14. Collect drug product release and stability data to reassess and lower the allowable number of sub-visible particles. A proposed specification including justification based on supporting data will be submitted as a CBE-0 supplement.

Final Report Submission:	September 2010
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15. Reassess release and shelf-life specifications for the ustekinumab drug substance and drug product within 2 years from the date of this letter and submit in an annual report.

Final Report Submission:

Annual Report 2011

16. Conduct end-of-life concurrent validation of Protein A, anion exchange, and cation exchange resins at the manufacturing scale. The studies will include an assessment of yield, chromatographic profile, and impurities where appropriate. Data will be submitted as a CBE-0 supplement.

Final Report Submission:

September 2011

17. Perform reduced scale end-of-life viral removal studies for the anion exchange resin. Study conditions will adequately reflect the manufacturing scale process.

Final Report Submission:

September 2010

18. Revise the direct product capture pool SDS-PAGE and IEF stability specifications upon review of available stability data. The proposed specifications, including justification based on supporting data, will be submitted as a CBE-0 supplement.

Final Report Submission:

September 2010

19. Develop and validate the Microflow Digital Imaging assay and incorporate this assay into the annual stability testing program with appropriately justified specifications. Alternately, documentation can be submitted to FDA demonstrating with due diligence that this assay could not be feasibly developed.

Final Report Submission:

September 2011

20. Perform both IEF and cIEF in parallel for future batches as part of the commercial stability program until sufficient data demonstrate that the cIEF is as stability indicating as the IEF. Data will be submitted as a CBE-30 supplement.

Final Report Submission:

September 2011

21. Perform an extensive qualification study for multi-use of the glass syringes which are used for pooling of vials for the visible particle assay to ensure continued effectiveness of the cleaning procedure. Data will be provided within one year of the date of this letter in an annual report.

Final Report Submission:

Annual Report 2010

22. Continue the root cause investigation to identify the causative factor(s) that led to increased visible particle counts on stability for the clinical and validation drug product batches. The final report will be provided within one year of the date of this letter in an annual report.

Final Report Submission:

Annual Report 2010

23. Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest (at disconnection of the final harvest bag for each Stage 3 batch) and harvest samples. The acceptance criteria for bioburden in-process controls should be consistent with historical data and reported as CFU/volume tested.

The revised test method and acceptance criteria including justification based on supporting data will be submitted as a prior approval supplement.

Final Report Submission:

September 2011

We request that you submit clinical protocols to your IND, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this BLA. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKETING COMMITMENT – FINAL STUDY REPORT**
- **POSTMARKETING COMMITMENT CORRESPONDENCE**
- **ANNUAL STATUS REPORT OF POSTMARKETING STUDY COMMITMENTS**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (<http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077374.pdf>) for further information.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on September 23, 2009, and amended and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

1. Evaluations of dermatologists/healthcare providers' understanding and patients' understanding of the risks of Stelara[™] (ustekinumab), including evaluations of the following:
 - a. Prescribers' understanding of the risks of Stelara[™] (ustekinumab), including the risks of serious infection, RPLS, and malignancy and how to select patients who are appropriate for treatment.
 - b. Patients' understanding of the risks of Stelara[™] (ustekinumab), including the risks of serious infection, RPLS, and malignancy.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.
4. A summary of all reported serious infections, RPLS, and malignancies with analysis of adverse event reporting by prescriber type (e.g., dermatologist, nurse, internist, oncologist), when available.
5. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) [or 21 CFR 601.70] and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125261 REMS ASSESSMENT

**NEW SUPPLEMENT FOR BLA 125261
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR BLA 125261
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

ADVERSE EVENT REPORTING

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). In addition, submit any adverse event reports related to malignancy, serious infections (including opportunistic infections and tuberculosis) and serious neurologic events as 15-day reports. Serious events are defined as events leading to death, hospitalization, disability, or reported as life threatening. You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

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>.

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 the 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, Office of Compliance, Division of Compliance Risk Management and Surveillance, 10903 New Hampshire Avenue, Bldg. 51, Room 4206, Silver Spring, MD 20993-0002.

CONTENT OF LABELING

Within 14 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling (text for the package insert and Medication Guide). For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved STN BL 125261/0.**" In addition, within 21 days of the date of this letter, amend your pending supplements for the Pre-Filled Syringe (STN BL 125261/1) with content of labeling in SPL format to include the changes approved in this BLA.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft 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 – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. 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 "**Product Correspondence – Final Printed Carton and Container Labels for approved STN BL 125261/0.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

If you have any questions, call the Regulatory Project Manager, Sue Kang, at 301-796-4216.

Sincerely,

/John Jenkins, M.D./ September 25, 2009
John Jenkins, M.D. on behalf of Julie Beitz, M.D.
Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Package Insert, Medication Guide, Carton and Container Labels
REMS (including Communication Plan)

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 use
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

STELARA™ is a human interleukin-12 and -23 antagonist indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. (1)

DOSAGE AND ADMINISTRATION

STELARA™ is administered by subcutaneous injection. (2)

- For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. (2.1)
- For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. (2.1)

DOSAGE FORMS AND STRENGTHS

- 45 mg/0.5 mL in a single-use glass vial (3)
- 90 mg/1 mL in a single-use glass vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Infections:** Serious infections have occurred. Do not start STELARA™ during any clinically important active infection. If a serious infection develops, stop 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) evaluation:** 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)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** One case was reported. If suspected, treat promptly and discontinue STELARA™. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence >3% and greater than with placebo): Nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Centocor Ortho Biotech Inc. at 1-800-457-6399 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Live vaccines:** Should not be given with STELARA™. (7.1)
- Concomitant therapy:** The safety of concomitant use of STELARA™ with immunosuppressants or phototherapy has not been evaluated. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

09/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

STELARA™ is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

STELARA™ is administered by subcutaneous injection.

- For patients weighing ≤ 100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

In subjects weighing >100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects [*see Clinical Studies (14)*].

The safety and efficacy of STELARA™ have not been evaluated beyond two years.

2.2 General Considerations for Administration

STELARA™ is intended for subcutaneous administration under the supervision of a physician.

Prior to administration, STELARA™ should be visually inspected for particulate matter and discoloration. STELARA™ is colorless to light yellow and may contain a few small translucent or white particles. STELARA™ should not be used if it is discolored or cloudy, or if other particulate matter is present. STELARA™ does not contain preservatives; therefore, any unused product remaining in the vial and/or syringe should be discarded.

It is recommended each injection be administered using a 27 gauge, ½ inch needle 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.

STELARA™ should only be administered by a healthcare provider. STELARA™ should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.

3 DOSAGE FORMS AND STRENGTHS

STELARA™ contains 90 mg ustekinumab per mL.

- 45 mg/0.5 mL in a single-use vial
- 90 mg/1 mL in a single-use vial

4 CONTRAINDICATIONS

None.

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)*].

STELARA™ should not be given to patients with any clinically important active infection. STELARA™ should not be administered until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. Exercise caution when considering the use of STELARA™ in patients with a chronic infection or a history of recurrent infection.

Serious infections requiring hospitalization occurred in the psoriasis development program. These serious infections included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract infections.

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™ will 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. 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. Patients receiving STELARA™ should be monitored closely 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.

5.5 Reversible Posterior Leukoencephalopathy Syndrome

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed during the clinical development program which included 3523 STELARA™-treated subjects. 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.

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, STELARA™ should be discontinued and appropriate treatment administered.

5.6 Immunizations

Prior to initiating therapy with STELARA™, patients should receive all immunizations appropriate for age 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.

5.7 Concomitant Therapies

The safety of STELARA™ in combination with other immunosuppressive agents or phototherapy has not been 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)].

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)]
- Reversible Posterior Leukoencephalopathy Syndrome [see *Warnings and Precautions* (5.5)]

6.1 Clinical Studies Experience

The safety data reflect exposure to STELARA™ in 2266 psoriasis subjects, including 1970 exposed for at least 6 months, 1285 exposed for at least one year, and 373 exposed for at least 18 months.

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.

Table 1 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 STUDY 1 and STUDY 2.

Table 1. Adverse reactions reported by $\geq 1\%$ of subjects through Week 12 in STUDY 1 and STUDY 2

	Placebo	STELARA™	
		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 drug reactions that occurred at rates less than 1% included: cellulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation). One case of RPLS occurred during clinical trials [see *Warnings and Precautions* (5.5)].

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 trials, 61% of STELARA™-treated subjects reported infections (1.24 per subject-year of follow-up). Serious infections were reported in 0.9% of subjects (0.01 per subject-year of follow-up).

Malignancies

In the controlled and non-controlled portions of psoriasis clinical trials, 0.4% of STELARA™-treated subjects reported malignancies excluding non-melanoma skin cancers (0.36 per 100 subject-years of follow-up). Non-melanoma skin cancer was reported in 0.8% of STELARA™-treated subjects (0.80 per 100 subject-years of follow-up) [see *Warnings and Precautions* (5.4)].

Serious malignancies included breast, colon, head and neck, kidney, prostate, and thyroid cancers.

Immunogenicity

The presence of ustekinumab in the serum can interfere with the detection of anti-ustekinumab antibodies resulting in inconclusive results due to assay interference. In STUDIES 1 and 2, antibody testing was done at time points when ustekinumab may have been present in the serum. Table 2 summarizes the antibody results from STUDIES 1 and 2. In STUDY 1 the last ustekinumab injection was between Weeks 28 and 48 and the last test for anti-ustekinumab antibodies was at Week 52. In STUDY 2 the last ustekinumab injection was at Week 16 and the last test for anti-ustekinumab antibodies was at Week 24.

Table 2

Antibody Results	STUDY 1 (N=743)	STUDY 2 (N=1198)
Positive	38 (5%)	33 (3%)
Negative	351 (47%)	90 (8%)
Inconclusive	354 (48%)	1075 (90%)

The data reflect the percentage of subjects whose test results were positive for antibodies to ustekinumab in a bridging immunoassay, 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.

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with STELARA™.

7.1 Live Vaccines

Live vaccines should not be given concurrently with STELARA™ [see *Warnings and Precautions* (5.5)].

7.2 Concomitant Therapies

The safety of STELARA™ in combination with immunosuppressive agents or phototherapy has not been evaluated [see *Warnings and Precautions* (5.6)].

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, TNF α , IFN) during chronic inflammation. Thus, ustekinumab could normalize the formation of CYP450 enzymes. A role for IL-12 or IL-23 in the regulation of CYP450 enzymes has not been reported. However, upon initiation of ustekinumab 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no studies of STELARA™ in pregnant women. STELARA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No teratogenic effects were observed in the developmental and reproductive toxicology studies performed in cynomolgus monkeys at doses up to 45 mg/kg ustekinumab, which is 45 times (based on mg/kg) the highest intended clinical dose in psoriasis patients (approximately 1 mg/kg based on administration of a 90 mg dose to a 90 kg psoriasis patient).

Ustekinumab was tested in two embryo-fetal development toxicity studies. Pregnant cynomolgus monkeys were administered ustekinumab at doses up to 45 mg/kg during the period of organogenesis either twice weekly via subcutaneous injections or weekly by intravenous injections. No significant adverse developmental effects were noted in either study.

In an embryo-fetal development and pre- and post-natal development toxicity study, three groups of 20 pregnant cynomolgus monkeys were administered subcutaneous doses of 0, 22.5, or 45 mg/kg ustekinumab twice weekly from the beginning of organogenesis in cynomolgus monkeys to Day 33 after delivery. There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, hematology, or serum biochemistry in dams. Fetal losses occurred in six control monkeys, six 22.5 mg/kg-treated monkeys, and five 45 mg/kg-treated monkeys. Neonatal deaths occurred in one 22.5 mg/kg-treated monkey and in one 45 mg/kg-treated monkey. No ustekinumab-related abnormalities were observed in the neonates from birth through six months of age in clinical signs, body weight, hematology, or serum biochemistry. There were no treatment-related effects on functional development until weaning, functional development after weaning, morphological development, immunological development, and gross and histopathological examinations of offsprings by the age of 6 months.

8.3 Nursing Mothers

Caution should be exercised when STELARA™ is administered to a nursing woman. The unknown risks to the infant from gastrointestinal or systemic exposure to ustekinumab should be weighed against the known benefits of breast-feeding. Ustekinumab is excreted in the milk of lactating monkeys administered ustekinumab. IgG is excreted in human milk, so it is expected that STELARA™ will be present in human milk. It is not known if ustekinumab is absorbed systemically after ingestion; however, published data suggest that antibodies in breast milk do not enter the neonatal and infant circulation in substantial amounts.

8.4 Pediatric Use

Safety and effectiveness of STELARA™ in pediatric patients have not been evaluated.

8.5 Geriatric Use

Of the 2266 psoriasis subjects exposed to STELARA™, a total of 131 were 65 years or older, and 14 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 4.5 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

STELARA™ is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, STELARA™ 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. STELARA™ is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

STELARA™ is available as: 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL. STELARA™ is supplied as a sterile solution in a single-use 2 mL Type I stoppered glass vial with a coated stopper. The STELARA™ solution is colorless to slightly yellow in appearance and has a pH of 5.7-6.3.

The 45 mg vial contains: 45 mg ustekinumab, 38 mg sucrose, 0.5 mg L-histidine, and 0.02 mg Polysorbate 80 to fill to a final volume of 0.5 mL.

The 90 mg vial contains: 90 mg ustekinumab, 76 mg sucrose, 1 mg L-histidine, and 0.04 mg Polysorbate 80 to fill to a final volume of 1 mL.

STELARA™ does not contain preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit used by both the interleukin (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-12 β1.

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 psoriatic subjects.

12.3 Pharmacokinetics

Absorption

In psoriasis subjects, 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 psoriasis subjects. Following multiple subcutaneous doses of STELARA™, the steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean ($\pm$ SD) steady-state trough serum concentration ranged from 0.31 ± 0.33 mcg/mL (45 mg) to 0.64 ± 0.64 mcg/mL (90 mg). There was

no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Distribution

Following subcutaneous administration of 45 mg (N=18) and 90 mg (N=21) of ustekinumab to psoriasis subjects, the mean ($\pm$ SD) apparent volume of distribution during the terminal phase (V_z/F) was 161 ± 65 mL/kg and 179 ± 85 mL/kg, respectively. The mean ($\pm$ SD) volume of distribution during the terminal phase (V_z) following a single intravenous administration to subjects with psoriasis ranged from 56.1 ± 6.5 to 82.1 ± 23.6 mL/kg.

Metabolism

The metabolic pathway of ustekinumab has not been characterized. As a human IgG1 κ monoclonal antibody ustekinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

The mean ($\pm$ SD) systemic clearance (CL) following a single intravenous administration of ustekinumab to psoriasis subjects ranged from 1.90 ± 0.28 to 2.22 ± 0.63 mL/day/kg. The mean ($\pm$ SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following intravenous and subcutaneous administration.

Weight

When given the same dose, subjects weighing >100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing ≤ 100 kg.

Hepatic and Renal Impairment

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

Elderly

A population pharmacokinetic analysis (N=106/1937 subjects 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.

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.

A male fertility study was conducted with only 6 male monkeys per group administered subcutaneous doses of 0, 22.5, or 45 mg/kg ustekinumab twice weekly prior to mating and during the mating period for 13 weeks, followed by a 13-week treatment-free period. Although fertility and pregnancy

outcomes were not evaluated in mated females, there were no treatment-related effects on parental toxicity or male fertility parameters.

A female fertility study was conducted in mice using an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, beginning 15 days before cohabitation and continuing through GD 7. There were no treatment-related effects on maternal toxicity or female fertility parameters.

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

Two multicenter, randomized, double-blind, placebo-controlled studies (STUDY 1 and 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.

STUDY 1 enrolled 766 subjects and 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 STUDY 1 and 40% of subjects in 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 study subjects had a history of psoriatic arthritis.

Clinical Response

The results of STUDY 1 and STUDY 2 are presented in Table 3 below.

Table 3. Clinical Outcomes STUDY 1 and STUDY 2

<u>Week 12</u>	<u>STUDY 1</u> STELARA™			<u>STUDY 2</u> STELARA™		
	<u>Placebo</u>	<u>45 mg</u>	<u>90 mg</u>	<u>Placebo</u>	<u>45 mg</u>	<u>90 mg</u>
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, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed >100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 4 below).

Table 4. Clinical Outcomes by Weight STUDY 1 and STUDY 2

	<u>STUDY 1</u> STELARA™			<u>STUDY 2</u> STELARA™		
	<u>Placebo</u>	<u>45 mg</u>	<u>90 mg</u>	<u>Placebo</u>	<u>45 mg</u>	<u>90 mg</u>
Subjects randomized	255	255	256	410	409	411
Week 12						
PASI 75 response						
≤ 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						
≤ 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

Subjects in STUDY 1 were evaluated through Week 52. At Week 40, those who were PASI 75 responders at both Weeks 28 and 40 were re-randomized 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

STELARA™ does not contain preservatives. STELARA™ is available in single-use vials containing 45 mg or 90 mg of ustekinumab.

The NDC number for the 45 mg vial is 57894-060-02.

The NDC number for the 90 mg vial is 57894-061-02.

Storage and Stability

Store STELARA™ upright and refrigerated at 2°C to 8°C (36°F to 46°F). Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. STELARA™ does not contain a preservative; discard any unused portion.

17 PATIENT COUNSELING INFORMATION

Instruct patients to read the Medication Guide before starting STELARA™ therapy and to reread the Medication Guide each time the prescription is renewed.

Infections

Inform patients that STELARA™ may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the doctor, and contacting their doctor if they develop any symptoms of infection.

Malignancies

Patients should be counseled about the risk of malignancies while receiving STELARA™.

Manufactured by Cilag AG,
Schaffhausen, Switzerland
for
Centocor Ortho Biotech Inc.
Horsham, PA 19044
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MEDICATION GUIDE
STELARA™ (stel ar' a)
(ustekinumab)
Injection

Read this Medication Guide before you start taking STELARA™ and each time before you get an injection. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment with STELARA™.

What is the most important information I should know about STELARA™?

STELARA™ is a medicine that affects your immune system. STELARA™ can increase your chances 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, sweats, or chills
- muscle aches
- cough
- shortness of breath
- blood in your 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 who has 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. It is not known if people who take STELARA™ will get any of these infections, because of the effects of STELARA™ on these proteins in your body.

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.

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).

STELARA™ may improve your psoriasis but may also lower the ability of your immune system to fight infections. This may also increase your risk for certain types of cancer.

It is not known if STELARA™ is safe and effective in children.

It is not known if taking STELARA™ for more than 2 years is safe and effective.

What should I tell my doctor before receiving STELARA™?

Before receiving 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™?”
- 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™.**
- receive phototherapy for your psoriasis.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if STELARA™ will harm your unborn baby. You and your doctor should decide if you will take STELARA™.
- are breast-feeding or plan to breast-feed. It is thought that STELARA™ passes into your breast milk. You should not breast-feed while taking STELARA™ without first talking with your doctor.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- other medicines that affect your immune system.
- certain medicines that can affect how your liver breaks down other medicines.

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

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

How will I receive STELARA™?

- STELARA™ is given by injection under the skin (subcutaneous injection).
- STELARA™ should only be given by a healthcare provider as directed by your doctor.
- Your doctor will decide the right dose of STELARA™ for you and how often you should receive it.
- Be sure to keep all of your scheduled follow-up appointments.

What should I avoid while receiving STELARA™?

You should not receive a live vaccine while taking STELARA™. See “What should I tell my doctor before taking STELARA™?”

What are the possible side effects of STELARA™?

STELARA™ can increase your chances of having serious side effects. See “What is the most important information I should know about STELARA™?”

Common side effects of STELARA™ include:

- upper respiratory infections
- headache
- tiredness

These are not all of the possible side effects of STELARA™. Tell your doctor about any side effect that bothers you or that does not go away. For more information, ask your doctor or pharmacist.

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

General information about STELARA™

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about STELARA™. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about STELARA™ that was written for healthcare professionals. For more information, go to www.STELARAinfo.com or call 1-800-457-6399.

What are the ingredients in STELARA™?

Active ingredient: ustekinumab

Inactive ingredients: sucrose, L-histidine, and polysorbate 80.

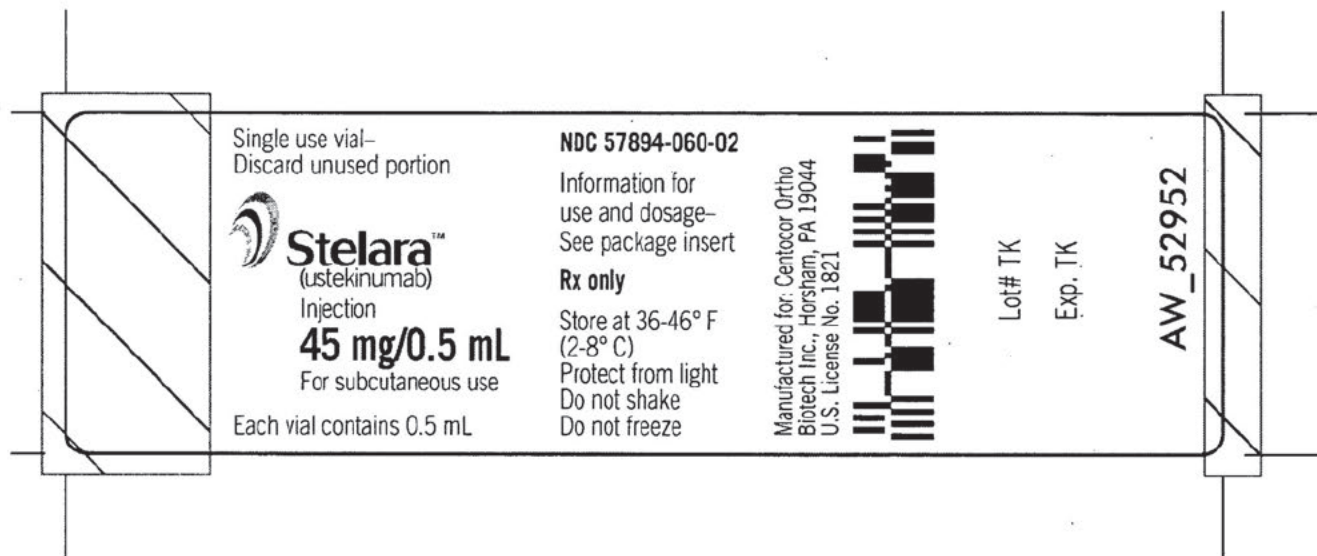
Manufactured by Cilag AG,
Schaffhausen, Switzerland
for
Centocor Ortho Biotech Inc.
Horsham, PA 19044

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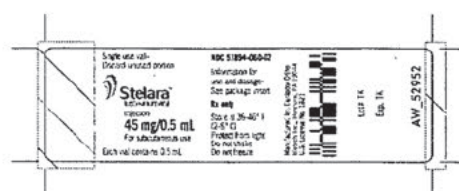
This Medication Guide has been approved by the U.S. Food and Drug Administration.

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45 mg version - 100%
FDA COMMENTS-RND 2



GPSG Global Pharmaceutical Supply Group

PRODUCT NAME Stelara COMPONENT TYPE Label
COMP. NUMBER AW_52952 ARTWORK VERSION 2
SOFTWARE USED Illustrator VERS. CS2 UPGRADE ☒
MODIFIED DATE 06/18/09 DESIGNER Kim DePaola
Date/Comment: TITLE BLOCK PROOFED ☐ NO ☒ YES

04/14/09: V1: CR created from 10139900 with revs per PDF.
06/18/09: V2: KD made revs per marked up PDF.

COLORS USED IN FILE



DIMENSIONS 2-13/64" x 21/32"

DWG # R/L/81924/V1 OUTPUT % 100%

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