

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125261

OTHER ACTION LETTER(s)



Our STN: BL 125261/0

COMPLETE RESPONSE

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

DEC 18 2008

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 STELARA (ustekinumab) for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

We acknowledge receipt of your amendments dated November 28, December 17, 2007, February 21, March 25 and 31, April 4, 10, 11, and 18, May 1, 13, 16, 21, 23, and 30, June 2, 6, 9, 11, 17, 19, 20, and 24, July 1, 10, 14, 15, 16, 17, 18, 28, and 30, August 8, 15, 18, and 21, September 24, October 15, 20, 21, 27, 29, and 30, and November 4, 2008.

We also acknowledge receipt of your amendments dated November 7 and 21, and December 8, 12, and 16, 2008, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. Before this application may be approved, you must address the following:

PRODUCT QUALITY

Deficiencies:

1. Control procedures need to be established to validate the performance of manufacturing processes responsible for causing variability in the drug product (§ 211.110). Specifically, numerous drug product lots have recently failed the visible particulate matter assay specification at release and during stability testing. The application lacks documentation of an event that can reasonably be determined to have caused the visible

particulate assay out-of-specification (OOS) results.

2. The application lacks an accurate testing and sampling method for measurement of visible particulate matter that has been developed, documented, reviewed, and approved by Centocor's Quality Control Unit (§ 211.165).

Information Needed for Resolution:

1. Identification of the root cause of the OOS results for the visible particulate assay supported by a comprehensive, consistent narrative of the investigation into the OOS events with data that strongly and directly support the conclusions. The root cause investigation should also outline corrective actions taken that ensure consistent drug product manufacture and testing.
2. Development and validation of a robust sampling and testing method for assessment of the level of visible particulates in the drug product. Development and validation results should provide assurance that the assay is able to consistently and reproducibly perform its intended function. The assay should be reviewed and approved by Centocor's Quality Control Unit.

Additional Requests and Comments:

1. Provide an analysis of the impact of changes to the sampling method for other assays that used pooled material, such as the sub-visible particulate method.
2. The IEF and cIEF assays need to be run side-by-side until sufficient data have been submitted to the Agency to demonstrate that the cIEF assay is as stability indicating as the IEF assay. These data should demonstrate that the cIEF assay would result in failures for stressed and accelerated stability samples at or before failures would occur due to the appearance of faint acidic bands seen by IEF method.
3. Both working cell banks _____, are **b(4)** suitable for use in manufacturing.

CLINICAL

Deficiencies:

STELARA (ustekinumab) is an immunosuppressant to be used chronically in psoriasis patients. Potential adverse events that may be related to the use of STELARA (ustekinumab) include serious infections and malignancy. Based on data from rodent models, there is a theoretical concern that blockade of IL-12/IL-23 may heighten patients' risk for malignancy. Humans genetically deficient in IL-12/IL-23 appear to have particular susceptibilities to infections from BCG, environmental mycobacteria, and non-typhoidal salmonella but no apparent excess risk for malignancy, although most of these patients have yet to reach middle age. There are no apparent signals for particular infection susceptibilities or malignancy in the safety database for STELARA (ustekinumab) submitted in support of the BLA; however, follow-up is only through 18 months.

Information Needed for Resolution:

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food Drug and Cosmetic Act (FDCA) to authorize 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)) and 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)). This provision took effect on March 25, 2008.

We have determined that a REMS is necessary for STELARA (ustekinumab) to ensure that its benefits outweigh the risks and that postmarketing clinical trials will be needed to further assess these risks.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for STELARA (ustekinumab) to ensure that the benefits of the drug outweigh the potential risks of serious infection and malignancy. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must contain the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that STELARA (ustekinumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of STELARA (ustekinumab). FDA has determined that STELARA (ustekinumab) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use STELARA (ustekinumab). FDA has also determined that STELARA (ustekinumab) is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who receive STELARA (ustekinumab) injections.

Communication Plan: We have determined that a communication plan to healthcare providers who are likely to prescribe and/or inject STELARA (ustekinumab) will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about the potential risks of serious infection and malignancy.

The communication plan must include, at minimum, the following:

1. Dear Healthcare Provider Letters to be distributed to dermatologists and other specialties expected to use STELARA (ustekinumab), chronically to treat psoriasis, if

the application is approved, to provide information about complications potentially associated with STELARA (ustekinumab). This letter should also inform healthcare providers about any available registries that may enroll patients treated with STELARA (ustekinumab).

2. An intensive adverse event reporting awareness campaign at major national meetings of appropriate specialties; if possible, develop and provide free-of-charge targeted CME programs covering the basic science underlying recommendations about infectious complications and the need for cancer surveillance.
3. A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the communication materials will be directed. These should include non-prescribers in specialties likely to be consulted for infectious or malignant adverse events.
4. A schedule for when and how these letters/materials are to be distributed to healthcare providers at the time STELARA (ustekinumab) is approved, and at specified intervals thereafter, if this application is approved.

Timetable for Assessments: The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than by 18 months, by 3 years and in the 7th year after the REMS is approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

Each assessment must assess the extent to which the elements of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

We suggest that your proposed REMS submission include two parts: a “Proposed REMS” and a “REMS Supporting Document.” Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for STELARA (ustekinumab). Additionally, all relevant proposed REMS materials, including educational and communication materials, should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include these documents as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for assessment of the REMS should include, but may not be limited to:

1. Results of evaluations addressing:
 - a. Prescribers’ understanding of the risks of STELARA (ustekinumab), including the risks of serious infection 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 and malignancy.

- c. Who is performing the STELARA (ustekinumab) injection in the healthcare setting (i.e., the physician/prescriber, nurse, patient, other).
 - d. How often patients are examined during STELARA (ustekinumab) therapy by a healthcare professional, and the type of professional performing the examination (i.e., physician/prescriber, physician/non-prescriber, nurse, other).
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 to address non-compliance.
 4. A report on the content, participation, and effectiveness of CME programs targeting prescribers and oncologists.
 5. A summary of all reported serious infections and malignancies, with analysis of adverse event reporting by prescriber type (e.g., dermatologist, nurse, internist, oncologist).
 6. 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.

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your BLA. Prominently identify the amendment containing the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

PROPOSED REMS FOR BLA 125261

On the first page of subsequent submissions related to the proposed REMS, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

BLA 125261 PROPOSED REMS – AMENDMENT

POSTMARKETING REQUIREMENTS UNDER 505(o)

In accordance with section 505(o)(3)(A), based on the signal of serious risk of serious infection and malignancy described above, we have determined that, if this application is approved, postmarketing clinical trials will be needed to further assess this risk.

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 signal of serious risk of developing serious infection or malignancy.

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 this signal of serious risk. Finally, we have determined that only clinical trials will be sufficient (rather than an observation study) to assess this risk of serious infection and malignancy through collection of

data on adverse events and laboratory assessments, including pharmacokinetic and immunogenicity parameters, in patients receiving long-term treatment with STELARA (ustekinumab).

Therefore, based on appropriate scientific data, FDA has determined that, if this application is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to continue the treatment of patients enrolled in the PHOENIX 1 and PHOENIX 2 trials for a total of 5 years. The specific details of these required postmarketing clinical trials will be described more fully in the approval letter for this application, if it is approved.

LABELING

We reserve comment on the proposed package insert until the application is otherwise adequate. If you revise labeling, your response must include updated 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>.

Submit draft carton and container labeling revised as follows:

- Add the following bolded statement or appropriate alternative per 21 CFR 208.24(d):
"ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical trials of the drug under consideration, regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
 - Present tabulations of the new safety data combined with the initial data.
 - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.
6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Your proposed tradename, STELARA, is acceptable.

Within 1 year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA guidance for industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products* (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

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

Sincerely,



Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research