

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761044Orig1s000

Trade Name: STELARA (ustekinumab) Injection 130 mg/26 mL

Generic or Proper Name: Ustekinumab

Sponsor: Janssen Biotech, Inc..

Approval Date: September 23, 2016

Indication: For the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker, or failed or were intolerant to treatment with one or more TNF blockers.

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CONTENTS

Reviews / Information Included in this NDA Review.

| | |
|--|----------|
| Approval Letter | X |
| Other Action Letters | |
| Labeling | X |
| REMS | |
| Summary Review | X |
| Officer/Employee List | X |
| Office Director Memo | |
| Cross Discipline Team Leader Review | X |
| Clinical Review(s) | X |
| Product Quality Review(s) | X |
| Non-Clinical Review(s) | X |
| Statistical Review(s) | X |
| Clinical Microbiology / Virology Review(s) | |
| Clinical Pharmacology Review(s) | X |
| Other Reviews | X |
| Risk Assessment and Risk Mitigation Review(s) | X |
| Proprietary Name Review(s) | X |
| Administrative/Correspondence Document(s) | X |

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RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



BLA 761044

BLA APPROVAL

Janssen Biotech, Inc.
Attention: Joseph Lallier
Associate Director, Global Regulatory Affairs
1400 McKean Road
P.O. Box 776
Spring House, PA 19477

Dear Mr. Lallier:

Please refer to your Biologics License Application (BLA) dated November 25, 2015, received November 25, 2015, submitted under section 351(a) of the Public Health Service Act for STELARA (ustekinumab) Injection 130 mg/26 mL.

LICENSING

We have approved your BLA for STELARA (ustekinumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, STELARA under your existing Department of Health and Human Services U.S. License No. 1864. STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker, or failed or were intolerant to treatment with one or more TNF blockers.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ustekinumab drug substance at Janssen Biologics B.V., Leiden, Einsteinweg 101, 2333 CB Leiden, The Netherlands and Janssen Biologics (Ireland), Barnahely, Ringaskiddy Co., Cork, Ireland. The final formulated product will be manufactured, filled, labeled, and packaged at Cilag AG, Hochstrasse 201, 8200 Schaffhausen, Switzerland. You may label your product with the proprietary name, STELARA, and will market it in 130 mg/26 mL Injection in single-dose vials.

DATING PERIOD

The dating period for STELARA shall be 24 months from the date of manufacture when stored at 2 – 8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of STELARA to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of STELARA, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Content of labeling must be identical to the enclosed labeling (text for the package insert, the patient package insert, and the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission

“Final Printed Carton and Container Labels for approved BLA 761044” Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for STELARA was not referred to a FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because an orphan designation was granted for your pediatric indication, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of malignancy and a known serious risk of opportunistic infections (such as tuberculosis [TB])

Furthermore, FDA has determined that the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess the known serious risks of malignancy and specific opportunistic infections (such as tuberculosis [TB]).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 3112-1 Conduct a long-term, postmarketing, observational study to assess the long-term safety of STELARA (ustekinumab) versus other therapies used in the treatment of adults with moderate to severe Crohn’s disease. The study’s primary outcome is malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (e.g., tuberculosis [TB]). Specify concise case definitions, and provide

outcome validation for both primary and secondary outcomes. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to ustekinumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate, with a pre-specified statistical analysis method. For the ustekinumab-exposed and comparator(s), the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure adequate number of patients with at least 18 months of ustekinumab exposure at the end of the study. Follow for a period of at least 7 years.

The timetable you submitted on September 22, 2016, states that you will conduct this study according to the following schedule:

| | |
|----------------------------|----------------|
| Draft Protocol Submission: | February 2017 |
| Final Protocol Submission: | September 2017 |
| Interim Report: | December 2025 |
| Study Completion: | August 2029 |
| Final Report Submission: | August 2030 |

Submit the protocol(s) to your IND 011632, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3112-2 Conduct a dose-ranging trial to determine the pharmacokinetics/pharmacodynamics, safety, and tolerability of STELARA (ustekinumab) induction dosing in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease despite conventional therapy.

The timetable you submitted on September 20, 2016, states that you will conduct this study according to the following schedule:

| | |
|----------------------------|---------------|
| Final Protocol Submission: | December 2016 |
| Study Completion: | February 2019 |
| Final Report Submission: | August 2019 |

- 3112-3 Conduct a randomized, controlled, blinded, multicenter trial to evaluate the safety and efficacy of STELARA (ustekinumab) in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease despite conventional therapy.

The timetable you submitted on September 22, 2016, states that you will conduct this study according to the following schedule:

| | |
|----------------------------|----------------|
| Draft Protocol Submission: | December 2019 |
| Final Protocol Submission: | June 2020 |
| Study Completion: | February 2024 |
| Final Report Submission: | September 2024 |

- 3112-4 Conduct a clinical trial to assess whether STELARA (ustekinumab) alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in Crohn's disease (CD) patients treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs).

The timetable you submitted on September 7, 2016, states that you will conduct this study according to the following schedule:

| | |
|----------------------------|----------------|
| Final Protocol Submission: | March 2017 |
| Trial Completion: | September 2019 |
| Final Report Submission: | March 2020 |

Submit clinical protocols to your IND 011632 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**,"

“Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

If you have any questions, call Lawrence Allan, Regulatory Project Manager, at (240) 402 – 2786.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
09/23/2016