BLA 761133

BLA APPROVAL

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Steffen Creaser, PhD
Associate Director, Global Regulatory Affairs Development, GI
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Creaser:

Please refer to your biologics license application (BLA) dated and received March 7, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Entyvio (vedolizumab) injection and Entyvio Pen (vedolizumab) injection, for subcutaneous use.

We acknowledge receipt of your resubmission dated March 27, 2023, which constituted a complete response to our December 17, 2019, action letter.

LICENSING

We have approved your BLA for Entyvio (vedolizumab) injection and Entyvio Pen (vedolizumab) injection effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Entyvio (vedolizumab) injection and Entyvio Pen (vedolizumab) injection under your existing Department of Health and Human Services U.S. License No. 1898. Entyvio (vedolizumab) injection and Entyvio Pen (vedolizumab) injection are indicated for treatment of adults with moderately to severely active ulcerative colitis (UC).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture subcutaneous vedolizumab drug substance at (b) (4) The final formulated prefilled syringe (PFS) drug product will be manufactured, filled, and packaged at (b) (4) The device will be assembled, labeled and packaged at Takeda Austria GmbH, Linz, Austria (FEI: 3001157285). You may label your product with the proprietary name, Entyvio, and market it in a single-dose PFS with needle safety device (108 mg/0.68 mL); you may label your product with the proprietary name, Entyvio Pen, and market it a single-dose prefilled pen (108 mg/0.68 mL).

DATING PERIOD

The dating period for Entyvio and Entyvio Pen shall be 18 months from the date of manufacture when stored at 5 °C ± 3°C, protected from light. The date of manufacture shall be defined as the date of final sterile filtration of the formulated PFS drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Entyvio and Entyvio Pen 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 Entyvio and Entyvio Pen, or in the manufacturing facilities, will require the submission of information to your BLA 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 with minor editorial revisions listed below and reflected in the enclosed labeling.

- Added the page header on page 2 and updated the page numbering throughout the Prescribing Information

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 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761133**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for vedolizumab was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class or in the intended population.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 waiving the pediatric study requirement for ages birth to <2 years because necessary studies are impossible or highly impracticable. This is because the incidence of ulcerative colitis in children ages birth to <2 years of age is very low.

We are deferring submission of your pediatric studies for ages ≥2 to <18 years of age years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by 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 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4493-2 A study to evaluate the pharmacokinetics, immunogenicity, and safety of Entyvio (vedolizumab) as a subcutaneous injection for maintenance treatment in pediatric patients ≥2 to <18 years of age with ulcerative colitis

or Crohn's disease who achieve clinical response following induction treatment with intravenous Entyvio (vedolizumab) for injection.

Final Protocol Submission: 10/2023
Study Completion: 06/2028
Final Report Submission: 12/2028

4493-3 A study to evaluate the long-term safety of Entyvio (vedolizumab) as a subcutaneous injection in pediatric subjects ≥2 to <18 years of age with ulcerative colitis or Crohn's disease.

Final Protocol Submission: 03/2024
Study Completion: 06/2033
Final Report Submission: 12/2033

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 118980, with a cross-reference letter to this BLA. Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4493-1 Perform a supplemental low endotoxin recovery study to examine the effects of (b) (4) at (b) (4) °C on endotoxin recovery in the drug product spiked with reference standard endotoxin or control standard endotoxin and stored up to (b) (4) days at (b) (4) °C.

The timetable you submitted on August 14, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit clinical protocols to your IND 118980 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/subjects 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. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

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

You must submit distribution reports under the distribution reporting requirements at 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:

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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 4207
Silver Spring, MD 20903

Your product is a combination product per 21 CFR Part 3. Therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at:https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products,

If you have any questions, contact Kelly Richards, Senior Regulatory Health Project Manager, at (240) 402-4276 or email at kelly.richards@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOYCE A KORVICK
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