BLA 761379/Original 2

BLA APPROVAL

Fresenius Kabi USA
Attention: Navayath Shobana, PhD
Senior Director, Regulatory Affairs Lead
Three Corporate Drive
Lake Zurich, IL 60047

Dear Dr. Navayath Shobana:

Please refer to your biologics license application (BLA) dated and received September 28, 2023, and your amendments, submitted under section 351(k) of the Public Health Service Act for Otulfi (ustekinumab-aauz) injection.

We acknowledge receipt of your amendment dated October 30, 2024, which constituted a request for approval following our September 27, 2024, provisional determination letter.

BLA 761379 initially provided for:

- Otulfi (ustekinumab-aauz) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use as biosimilar to and interchangeable with Stelara (ustekinumab) injection 45 mg/0.5 mL single-dose prefilled syringe for subcutaneous use,

- Otulfi (ustekinumab-aauz) injection 90 mg/1.0 mL single-dose prefilled syringe for subcutaneous use as biosimilar to and interchangeable with Stelara (ustekinumab) injection 90 mg/1.0 mL single-dose prefilled syringe for subcutaneous use, and

- Otulfi (ustekinumab-aauz) injection 130 mg/26 mL single-dose vial for intravenous use as biosimilar to and interchangeable with Stelara (ustekinumab) injection 130 mg/26 mL single-dose vial for intravenous use.

For administrative purposes, BLA 761379 was split as follows:

- BLA 761379/Original 1 – biosimilarity
- BLA 761379/Original 2 – interchangeability

The subject of this correspondence is BLA 761379/Original 2. A separate correspondence was issued for BLA 761379/Original 1 on September 27, 2024.

LICENSING

We have approved BLA 761379/Original 2 for Otulfi (ustekinumab-aauz) as interchangeable biosimilar products effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Otulfi, under your existing Department of Health and Human Services U.S. License No. 2146.

Otulfi (ustekinumab-aauz) is indicated for the treatment of:

Adult patients with:

- moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis (PsA)
- moderately to severely active Crohn's disease (CD)
- moderately to severely active Ulcerative colitis (UC)

Pediatric patients 6 years and older with:

- moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis (PsA)

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ustekinumab-aauz drug substance at (b) (4). The final formulated drug product for the 45 mg/0.5 mL and 90 mg/1.0 mL prefilled syringes will be manufactured and filled at (b) (4), and assembled, labeled and packaged at (b) (4). The final formulated drug product for the 130 mg/26 mL vial will be manufactured and filled at (b) (4), and labeled and packaged at (b) (4). You may label your product with the proprietary name, Otulfi, and market it as 45 mg/0.5 mL injection in a single-dose prefilled syringe and 90 mg/1.0 mL injection in a single-dose prefilled syringe for subcutaneous injection, and as 130 mg/26 mL injection in a single-dose vial for intravenous use.

DATING PERIOD

The dating period for Otulfi prefilled syringe shall be 36 months from the date of manufacture when stored at 5°C ± 3°C, protected from light. The dating period for Otulfi vial presentation shall be 24 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 drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4)

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

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Otulfi 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 Otulfi, 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.

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]

The SPL will be accessible via publicly available labeling repositories.

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

[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 claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

At this time, no pediatric assessment will be required under PREA.

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

We remind you of your postmarketing commitments:

4707 -2 Perform a real-world commercial shipping validation study to confirm the suitability of shipping container and transportation method with respect to maintaining intended product temperature, package integrity, and product quality of the Otulfi drug product, stored in a vial (5 mg/mL) and pre-filled syringe (90 mg/mL), based on the worst case scenario.

The timetable you submitted on September 4, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2025

4707-3 Perform an additional study(ies) to support the control limits for (b) (4) FYB202 90 mg/mL pre-filled syringe drug product batch. The study should be designed to support worst-case (b) (4) using FYB202 DS batches (b) (4) Submit the results in a final study report to the BLA.

The timetable you submitted on August 26, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2025

4707-4 Implement pressure monitoring during sterilizing filtration of FYB202 5 mg/mL vial drug product (DP) and update Sections 3.2.P.3.3 and 3.2.P.3.4 of the BLA (b) (4)

The timetable you submitted on May 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2025

4707-5 Validate and implement a container closure integrity test (CCIT) method [redacted] (b) (4)

The timetable you submitted on June 12, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

4707-6 Conduct a minimum load sterilization validation study with three runs [redacted] (b) (4)

The timetable you submitted on June 12, 2024, states that you will conduct this stud according to the following schedule:

Final Report Submission: 12/2024

4707-7 Validate and implement an alternative quantitative bacterial endotoxin method not subject to low endotoxin recovery to replace the USP <151> pyrogen test for FYB 202 5 mg/mL vial DP release.

The timetable you submitted on May 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2025

4707-8 Revalidate the blue dye ingress CCIT method to demonstrate the CCIT method is reliable for use (i.e., all positive controls show positive results) for FYB202 drug product pre-filled syringe (PFS) 45 mg in 0.5 mL and FYB202 DP PFS 90 mg in 1.0 mL.

The timetable you submitted on May 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

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*.[3]

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 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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:

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:

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] 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
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

Your product is a Part 3 combination product (21 CFR 3.2(e)); 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 FDA.gov.

If you have any questions, contact Chau Nguyen, Regulatory Project Manager at chau.nguyen@fda.hhs.gov or (240)-402-0022.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director of Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

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/

TATIANA OUSSOVA
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