BLA 761255/Original 1

BLA APPROVAL

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047

Attention: Navayath Shobana, PhD
Director, Regulatory Affairs

Dear Dr. Shobana:[1]

Please refer to your biologics license application (BLA) dated and received December 13, 2021, and your amendments, under section 351(k) of the Public Health Service Act for Idacio (adalimumab-aacf), 40 mg/0.8 mL.

BLA 761255 provides for the use of Idacio (adalimumab-aacf) for the following indications including:

1. Rheumatoid Arthritis (RA): reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
2. Juvenile Idiopathic Arthritis (JIA):reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years and older.
3. Psoriatic Arthritis (PsA): reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
4. Ankylosing Spondylitis (AS): reducing signs and symptoms in adult patients with active AS.
5. Crohn's Disease (CD): treatment of moderately to severely active Crohn's disease in adult and pediatric patients 6 years of age and older.
6. Ulcerative Colitis (UC): treatment of moderately to severely active ulcerative colitis in adult patients.
7. Plaque Psoriasis (Ps): treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

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

For administrative purposes, we have designated as follows:

- BLA 761255/Original 1 – single-dose prefilled pen and single-dose prefilled glass syringe

(b) (4)

LICENSING

We have approved your BLA for Idacio (adalimumab-aacf) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Idacio (adalimumab-aacf) under your existing Department of Health and Human Services U.S. License No. 2146. Idacio (adalimumab-aacf) is indicated for the indications listed above.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture adalimumab-aacf drug substance at (b) (4). The final formulated product will be manufactured and filled at (b) (4) and assembled, labeled and packaged at (b) (4). You may label your product with the propietary name, Idacio, and will market it in a 40 mg/0.8 mL injection in a single-dose prefilled syringe and a 40 mg/0.8 mL injection in a single-dose prefilled pen.

DATING PERIOD

The dating period for Idacio shall be 36 months from the date of manufacture when stored at 2 to 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 your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

Any changes in the manufacturing, testing, packaging, or labeling of Idacio, 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.

FDA LOT RELEASE

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

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[2] 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.*[3]

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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761255**." Approval of this submission by FDA is not required before the labeling is used.

[2] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[3] 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.

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.

Rheumatoid Arthritis

At this time, we have determined that, with respect to Polyarticular Juvenile Idiopathic Arthritis (pJIA) in pediatric patients 0 to less than 2 years of age, no pediatric studies will be required under PREA for your BLA.

Psoriatic Arthritis

At this time, we have determined that, with respect to this indication, no pediatric studies will be required under PREA for your BLA.

Ankylosing Spondylitis

At this time, we have determined that, with respect to this indication, no pediatric studies will be required under PREA for your BLA.

Crohn's Disease

At this time, we have determined that, with respect to this indication, no pediatric studies will be required under PREA for your BLA.

Ulcerative Colitis

At this time, we have determined that, with respect to UC in pediatric patients 0 to less than 5 years of age, no pediatric studies will be required under PREA for your BLA. You have provided a pediatric assessment for UC in pediatric patients 5 years of age and older, and nothing further is required at this time.

Plaque Psoriasis

At this time, we have determined that, with respect to this indication, no pediatric studies will be required under PREA for your BLA.

Age-appropriate presentation

We are deferring the required pediatric assessment for patients < 40 kg. See Deferred Pediatric Assessments below.

Deferred Pediatric Assessments

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

4376-1 Develop a presentation that can be used to accurately administer Idacio (adalimumab-aacf) to pediatric patients weighing 10 kg to less than 40 kg.

The timetable you submitted on December 5, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2024

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

We remind you of your postmarketing commitments:

4376-2 To repeat the bacterial retention study (b) (4) .

The timetable you submitted on May 20, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: January 2023

4376-3 To repeat the sterilization validation (b) (4)

The timetable you submitted on October 20, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: January 2023

4376-4 To update the drug substance and drug product release and stability specifications for MSB11022 to include control for purity (monomer) by SE-HPLC and purity (main peak) by non-reduced CE-SDS with appropriately justified acceptance criteria. The updated drug substance and drug product release and stability specifications, method validation data, and other supporting data will be submitted to the BLA per 21 CFR 601.12.

The timetable you submitted on December 8, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2023

4376-5 To update the drug substance and drug product release specifications for MSB11022 to include justified analytical thresholds for new peaks detected by the peptide mapping and icIEF identity tests. The updated release acceptance criteria, method validation data, and other supporting information will be submitted to the BLA per 21 CFR 601.12.

The timetable you submitted on December 8, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2023

4376-6 To update the system suitability testing and criteria for the protein content by O.D. analytical method in the MSB11022 specifications. The updated method procedure, system suitability criteria, and supporting studies will be submitted to the BLA per 21 CFR 601.12.

The timetable you submitted on December 8, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2023

4376-7 To revise the in process control (IPC) acceptance criteria [redacted] (b) (4) to ensure meeting the label claim. The updated IPC acceptance criteria and supporting studies and data will be submitted to the BLA per 21 CFR 601.12.

The timetable you submitted on December 8, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2023

4376-8 To implement identity test(s) for final MSB11022 drug product assembled in the prefilled syringe with the autoinjector (b) (4) devices after labeling and secondary packaging per 21CFR 610.14. The identity test(s) will distinguish MSB11022 drug product (b) (4) proposed for the US market from the (b) (4) drug product if manufactured at the same facility. The final identity test and supporting information will be submitted to the BLA per 21 CFR 601.12.

The timetable you submitted on December 8, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2023

Submit clinical protocols to your IND 124098 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]

[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

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (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 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 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, call Susie Choi, Regulatory Project Manager, at 240-402-2925.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
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
- 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/

NIKOLAY P NIKOLOV
12/13/2022 01:42:00 PM