



BLA 761071

## BLA APPROVAL

Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540

Attention: Bijal Pandhi, PharmD  
Associate Director, Regulatory Strategy and Science

Dear Dr. Pandhi:

Please refer to your Biologics License Application (BLA) dated October 30, 2017, received October 30, 2017, and your amendments, submitted under section 351(k) of the Public Health Service Act for Hyrimoz (adalimumab-adaz) injection, 40 mg/0.8 mL for subcutaneous administration.

### LICENSING

We have approved your BLA for Hyrimoz (adalimumab-adaz) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Hyrimoz under your existing Department of Health and Human Services U.S. License No. 2003. Hyrimoz is indicated for:

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 rheumatoid arthritis.
2. Juvenile Idiopathic Arthritis (JIA):
  - Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age 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 psoriatic arthritis.
4. Ankylosing Spondylitis (AS):
  - Reducing signs and symptoms in adult patients with active ankylosing spondylitis.

5. Adult Crohn's Disease (adult CD):

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
- Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

6. Ulcerative Colitis (UC):

- Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP).

7. Plaque Psoriasis (PsO):

- The 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.

### **MANUFACTURING LOCATIONS**

Under this license, you are approved to manufacture adalimumab-adaz drug substance at Sandoz GmbH Schaftenau in Langkampfen, Austria, and (b) (4). The final formulated drug product will be manufactured, filled, and packaged at (b) (4); assembled, labeled, and packaged at (b) (4). You may label your product with the proprietary name, Hyrimoz, and will market it in 40 mg/0.8 mL injection, in a single-dose prefilled syringe or a single-dose autoinjector.

### **DATING PERIOD**

The dating period for Hyrimoz 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. 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 protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

### **FDA LOT RELEASE**

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

### **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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Medication Guide, and Instructions for Use). 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 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761071.**” Approval of this submission by FDA is not required before the labeling is used.

### **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.

The following comments pertain to Rheumatoid Arthritis indication:

We are waiving the pediatric studies requirement for the Polyarticular Juvenile Idiopathic Arthritis (pJIA) in pediatric patients 0 to less than 2 years of age because necessary studies are impossible or highly impracticable given that the disease is rarely diagnosed in this population.

We are deferring the required pediatric assessment for pediatric patients 2 years to less than 4 years of age. See Deferred Pediatric Assessments below.

We are deferring the required pediatric assessment for patients < 30 kg. See Deferred Pediatric Assessments below.

The following comment pertains to Psoriatic Arthritis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because necessary studies are impossible or highly impracticable.

The following comment pertains to Ankylosing Spondylitis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because necessary studies are impossible or highly impracticable.

The following comments pertain to Crohn's Disease indication:

We are waiving the pediatric study requirements for pediatric patients with Crohn's disease less than 6 years of age because necessary studies for this product are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

We are deferring the required pediatric assessment for pediatric patients 6 years to 17 years of age. See Deferred Pediatric Assessments below.

The following comments pertain to Ulcerative Colitis indication:

We are waiving the pediatric study requirements for pediatric patients with ulcerative colitis less than 5 years of age because necessary studies for this product are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

We are deferring the required pediatric assessment for pediatric patients 5 to 17 years of age. See Deferred Pediatric Assessments below.

The following comment pertains to Plaque Psoriasis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.

### **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.

3506-1            Assessment of Hyrimoz (adalimumab-adaz) for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 to less than 4 years of age

The timetable you submitted on October 19, 2018, states that you will conduct this study according to the following schedule:

Final report submission date:            September 2021

3506-2            Assessment of Hyrimoz (adalimumab-adaz) for the treatment of pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age

The timetable you submitted on October 19, 2018, states that you will conduct this study according to the following schedule:

Final report submission date:            September 2021

3506-3            Assessment of Hyrimoz (adalimumab-adaz) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age

The timetable you submitted on October 19, 2018, states that you will conduct this study according to the following schedule:

Final report submission date:            December 2020

3506-4            Develop a presentation that can be used to accurately administer Hyrimoz (adalimumab-adaz) to pediatric patients who weigh less than 30 kg

The timetable you submitted on October 19, 2018, states that you will conduct this study according to the following schedule:

Final report submission date:            September 2021

Submit the protocols to your IND 115732, 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 commitments:

3506-5 To qualify the bioburden test method for the (b) (4) samples at Sandoz Schaftenau using 10 mL test volumes. Submit the qualification report as a CBE-0 supplement in accordance with 21 CFR 601.12(c)(5).

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

3506-6 To qualify the bioburden test for the (b) (4) using the (b) (4) and implement the new bioburden test method. Submit the qualification report as a CBE-30 supplement in accordance with 21 CFR 601.12(c).

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

3506-7 To develop and implement a comprehensive and robust control strategy to control for effector function of adalimumab-adaz drug substance at release. Submit the proposed specification as a Prior Approval Supplement in accordance with 21 CFR 601.12(b).

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

3506-8 To implement an apoptosis inhibition assay for release and shelf life testing of adalimumab-adaz drug substance and drug product. Submit the proposed

specification as a Prior Approval Supplement in accordance with 21 CFR 601.12(b).

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2019

3506-9 To conduct a drug product (DP) transport validation study during summer time, shipping DP from [REDACTED] (b) (4)

The timetable you submitted on October 18, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2018

Submit clinical protocols to your IND 115732 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 Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) 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).

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

## **BsUFA II APPLICANT INTERVIEW**

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs under BsUFA II ('the Program'). The BsUFA II Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a BsUFA II applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Sally Seymour, MD  
Acting Director  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURES:

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

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**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.**  
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/s/  
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NIKOLAY P NIKOLOV

10/30/2018

Signed under the authority delegated by Dr. Sally Seymour, Acting Division Director,  
DPARP.