DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761042

BLA APPROVAL

Sandoz Inc.
100 College Road West
Princeton, NJ 08540

Attention: Jordanis Joy, PharmD
Regulatory Affairs Associate

Dear Dr. Joy:

Please refer to your Biologics License Application (BLA) dated July 30, 2015, received July 30, 2015, and your amendments, submitted under section 351(k) of the Public Health Service Act for Erelzi (etanercept-szzs) Injection 25 mg/0.5 mL and 50 mg/mL.

We also refer to our approval letter dated August 30, 2016, which you stated contained the following errors:

1. Manufacturing Locations
2. Dating Period
3. Manufacturing Date
4. Required pediatric Assessments

This replacement approval letter incorporates appropriate correction of the above named errors.

The effective approval date will remain August 30, 2016, the date of the original approval letter.

We acknowledge receipt of your major amendment dated April 28, 2016, which extended the goal date by three months.

LICENSING

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

- Rheumatoid Arthritis (RA)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)

- Plaque Psoriasis (PsO) in adults

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture etanercept-szzs drug substance at Sandoz GmbH in Langkampfen, Austria. The final formulated product will be manufactured, filled, and packaged at Novartis Pharma Stein AG, Stein, Switzerland. The device will be assembled, packaged, and labeled at IDT Biologika, Dessau-Rosslau, Germany. You may label your product with the proprietary name, Erelzi, and will market it in single-dose prefilled syringes containing 25 mg/0.5 mL or 50 mg/mL Injection and single-dose prefilled Sensoready Pens containing 50 mg/mL Injection.

DATING PERIOD

The dating period for Erelzi 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 Erelzi 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 Erelzi, 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, text for the patient package insert, 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.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

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 761042**." 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.

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.

We are waiving the pediatric studies requirement for the following indications:

- Psoriatic Arthritis because necessary studies are impossible or highly impracticable.
- Ankylosing Spondylitis because necessary studies are impossible or highly impracticable.
- Plaque Psoriasis because there is evidence strongly suggesting that the product would be unsafe in all pediatric age groups

We are waiving the pediatric study requirement for Polyarticular Juvenile Idiopathic Arthritis (pJIA) for ages 0 to 1 year 11 months because necessary studies are impossible or highly impracticable. This is because there are too few children with pJIA to study.

We are deferring submission of your pediatric study for pJIA for pediatric patients who weigh less than 63 kg for this application because development of a pediatric presentation is not complete.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

3110-1 Develop a presentation that can be used to accurately administer etanercept-szzs to pediatric patients who weigh less than 63 kg.

Final Report Submission: December 2019

Reports of this required pediatric postmarketing study 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:

3110-2 Develop and implement an analytical method for release and stability testing of GP2015 drug substance and drug product that can adequately assess levels of hydrophobic variants, including wrongly bridged disulfide bond variants. Submit the method final validation report and the release and stability acceptance criteria as a Prior Approval Supplement.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2017

3110-3 Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (e,g., surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced

exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. Submit the final report as a Changes Being Effected in 30 days (CBE30) and include any change in filtration parameters based upon the study.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2017

3110-4 Use a validated method to measure break loose, glide force (BLGF) for (b) (4) drug product pre-filled syringes to generate data from commercial batches to define release specifications for BLGF. Submit the study report and specifications for BLGF including testing site in the annual report.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2019

3110-5 Develop methods for confirming the injection depth (e.g. needle length exposed for injection), audible feedback (e.g. occurrence of second click) and visual feedback (e.g. plunger fills the window and stops moving) for release testing. Define release specifications that meet design output specifications for injection depth, audible feedback, and visual feedback for lot release testing prior to launch of Erelzi. Submit the study report and release specifications in the annual report.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2017

3110-6 Complete transport validation testing to assess mechanical stress on the new folding box and transport carton prior to launch of Erelzi. Submit the final transport validation report.

The timetable you submitted on August 18, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2016

Submit clinical protocols to your IND 114187 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 Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,
{See appended electronic signature page}
Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
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/

BADRUL A CHOWDHURY
08/30/2016