



BLA 761143

BLA APPROVAL

Horizon Therapeutics Ireland DAC
c/o Horizon Pharma USA, Inc.
Attention: Nicole Potthast, RN, BSN, MBA
Director, Regulatory Affairs
150 South Saunders Road
Lake Forest, IL 60045

Dear Ms. Potthast:

Please refer to your biologics license application (BLA) dated July 6, 2019, received July 8, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tepezza (teprotumumab-trbw) Injection, 500 mg.

LICENSING

We have approved your BLA for Tepezza (teprotumumab-trbw) effective on the date of this letter for use as recommended in the enclosed agreed-upon labeling. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Tepezza under your existing Department of Health and Human Services U.S. License No. 2022. Tepezza is indicated for treatment of thyroid eye disease.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture teprotumumab drug substance at

[REDACTED] (b) (4).

The final formulated drug product will be manufactured, filled, labeled, and packaged [REDACTED] (b) (4). You may label your product with the proprietary name, Tepezza, and market it in 500 mg single-dose vials for injection.

DATING PERIOD

The dating period for Tepezza shall be 18 months from the date of manufacture when stored at 5±10°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 [REDACTED] (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 21 CFR 601.12.

FDA LOT RELEASE

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

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.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). 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*.² 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 761143.**” 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. Because this biological product for this indication has orphan drug designation, this requirement is not applicable.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct post-marketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

¹ <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>.

We have determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a risk from extended dosing and from repeated courses of treatment. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies according to the following schedules:

- 3780-8 A descriptive clinical trial to evaluate the safety, efficacy and need for retreatment of three different teprotumumab treatment durations for the treatment of Thyroid Eye Disease.

Final Protocol Submission: 08/2020
First Patient Enrolled: 01/2021
Study Completion: 05/2026
Final Report Submission: 11/2026

- 3780-9 Completion of the ongoing study, HZNP-TEP-302 (OPTIC-X).

Study Completion: 07/2020
Final Report Submission: 01/ 2021

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your post-marketing commitments, with the timetable you submitted on January 6, 2020, which states that you will conduct these studies according to the following schedules:

- 3780-1 Establish an in-house qualification program for the IGF-1R AlphaLISA commercial kit used to control the potency of teprotumumab drug substance and drug product at release and during storage. Submit the description of the qualification program, information and data to support the adequacy of the qualification program with respect to the assurance of consistent performance of the AlphaLISA commercial kit in final study report.

Final Report Submission: 03/2020

- 3780-2 Re-validate the potency assay using the IGF-1R AlphaLISA commercial kit to ensure proper implementation of an internal assay control. Submit the updated potency assay description, information and data to support the validation of the updated potency assay in a PAS to the BLA.

Final Report Submission: 02/2020

- 3780-3 Develop, validate, and implement an in-house biological activity assay to control the potency for lot release and stability testing of teprotumumab drug substance and drug product. Submit the analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion for the in-house potency assay to the BLA in a PAS.

Final Report Submission: 07/2021

- 3780-4 Perform (b) (4) testing (b) (4) of three consecutive commercial batches to confirm the consistency of the protein concentration values for the filled vials throughout (b) (4). Submit the (b) (4) testing results in a final study report.

Final Report Submission: 05/2020

- 3780-5 Perform real-time drug product container closure system leachable studies using appropriate methods to detect, identify, and quantify organic non-volatile, volatile, and semi-volatile species and metals through the end of shelf life. Submit the complete data set and toxicology risk evaluation for the levels of leachables detected in the drug product in a final study report.

Final Report Submission: 12/2020

- 3780-6 Develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay for teprotumumab drug substance release. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30 to the BLA.

Final Report Submission: 06/2021

- 3780-7 Validate the (b) (4) teprotumumab drug product (b) (4) and submit the validation data.

Final Report Submission: 06/2020

Submit clinical protocol(s) to your IND 112952 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

Required Post-marketing Protocol Under 505(o), Required Post-marketing Final Report Under 505(o), Required Post-marketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any post-marketing commitments or required studies or clinical trials. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of post-marketing 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 Patient Package Insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.³ Information and Instructions for completing the form can be found at FDA.gov.⁴ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁵

³ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁵ <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

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Peter Stein, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - 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/

PETER P STEIN
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