

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**761143Orig1s023**

*Trade Name:* TEPEZZA

*Generic or Proper Name:* teprotumumab-trbw

*Sponsor:* Horizon Therapeutics Ireland DAC

*Approval Date:* July 17, 2023

*Indication:* TEPEZZA is an insulin-like growth factor-1 receptor inhibitor indicated for the treatment of Thyroid Eye Disease

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 761143Orig1s023

### CONTENTS

#### Reviews / Information Included in this NDA Review.

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letters</b>	
<b>Labeling</b>	<b>X</b>
<b>REMS</b>	
<b>Summary Review</b>	
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Clinical Review(s)</b>	
<b>Product Quality Review(s)</b>	
<b>Non-Clinical Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Clinical Microbiology / Virology Review(s)</b>	
<b>Clinical Pharmacology Review(s)</b>	
<b>Other Reviews</b>	<b>X</b>
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

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**APPROVAL LETTER**

BLA 761143/S-023

## SUPPLEMENT APPROVAL

Horizon Therapeutics Ireland DAC  
c/o Horizon Therapeutics USA Inc  
Attention: Fred Henry, MS, MPH  
Senior Director, Regulatory Affairs  
1 Horizon Way  
Deerfield, IL 60015

Dear Fred Henry:

Please refer to your supplemental biologics license application (sBLA), dated and received January 20, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for TEPEZZA (teprotumumab-trbw) for injection. This Prior Approval sBLA provides for additions to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and PATIENT COUNSELING INFORMATION sections of the Prescribing Information.

### **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, as described at FDA.gov,<sup>1</sup> that is identical to the enclosed labeling (text for the Prescribing Information) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. 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*.<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> 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>.

If you have any questions about this supplement, call Derek Alberding, Clinical Analyst, at (240) 402-0963.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, MD  
Director  
Division of Ophthalmology  
Office of Specialty Medicine  
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

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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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WILEY A CHAMBERS  
07/17/2023 03:50:00 PM

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**761143Orig1s023**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use TEPEZZA safely and effectively. See full prescribing information for TEPEZZA.

**TEPEZZA (teprotumumab-trbw) for injection, for intravenous use**  
**Initial U.S. Approval: 2020**

**RECENT MAJOR CHANGES**

Indications and Usage (1)	4/2023
Warnings, and Precautions,	
Hyperglycemia (5.3)	12/2022
Hearing Impairment Including Hearing Loss (5.4)	7/2023

**INDICATIONS AND USAGE**

TEPEZZA is an insulin-like growth factor-1 receptor inhibitor indicated for the treatment of Thyroid Eye Disease (1)

**DOSAGE AND ADMINISTRATION**

- Initiate dosing with 10 mg/kg for first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions (2.1)
- Administer TEPEZZA by intravenous infusion over 60 to 90 minutes (2.3)

**DOSAGE FORMS AND STRENGTHS**

For Injection: 500 mg lyophilized powder in a single-dose vial for reconstitution (3)

**CONTRAINDICATIONS**

None (4)

**WARNINGS AND PRECAUTIONS**

- **Infusion Reactions:** If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management (5.1)
- **Exacerbation of Preexisting Inflammatory Bowel Disease (IBD):** Monitor patients with preexisting IBD for flare of disease; discontinue TEPEZZA if IBD worsens (5.2)
- **Hyperglycemia:** Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving TEPEZZA (5.3)
- **Hearing Impairment Including Hearing Loss:** TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients (5.4)

**ADVERSE REACTIONS**

Most common adverse reactions (incidence greater than 5%) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dry skin, dysgeusia, headache, weight decreased and nail disorder (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon at 1-866-479-6742 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**USE IN SPECIFIC POPULATIONS**

Females of Reproductive Potential: Appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2023

**FULL PRESCRIBING INFORMATION: CONTENTS\***

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
  - 2.1 Recommended Dosing
  - 2.2 Reconstitution and Preparation
  - 2.3 Administration
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
  - 5.1 Infusion Reactions
  - 5.2 Exacerbation of Preexisting Inflammatory Bowel Disease
  - 5.3 Hyperglycemia
  - 5.4 Hearing Impairment Including Hearing Loss
- 6 ADVERSE REACTIONS**
  - 6.1 Clinical Trials Experience
  - 6.2 Immunogenicity
  - 6.3 Postmarketing Experience

- 8 USE IN SPECIFIC POPULATIONS**
  - 8.1 Pregnancy
  - 8.2 Lactation
  - 8.3 Females and Males of Reproductive Potential
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
  - 12.1 Mechanism of Action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
  - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosing

The recommended dose of TEPEZZA is an intravenous infusion of 10 mg/kg for the initial dose followed by an intravenous infusion of 20 mg/kg every three weeks for 7 additional infusions.

#### 2.2 Reconstitution and Preparation

Step 1: Calculate the dose (mg) and determine the number of vials needed for the 10 or 20 mg/kg dosage based on patient weight. Each TEPEZZA vial contains 500 mg of the teprotumumab antibody.

Step 2: Using appropriate aseptic technique, reconstitute each TEPEZZA vial with 10 mL of Sterile Water for Injection, USP. Ensure that the stream of diluent is not directed onto the lyophilized powder, which has a cake-like appearance. Do not shake, but gently swirl the solution by rotating the vial until the lyophilized powder is dissolved. The reconstituted solution has a volume of 10.5 mL. Withdraw 10.5 mL of reconstituted solution to obtain 500 mg. After reconstitution, the final concentration is 47.6 mg/mL.

Step 3: The reconstituted TEPEZZA solution must be further diluted in 0.9% Sodium Chloride Injection, USP prior to infusion. To maintain a constant volume in the infusion bag, a sterile syringe and needle should be used to remove the volume equivalent to the amount of the reconstituted TEPEZZA solution to be placed into the infusion bag. Discard the 0.9% Sodium Chloride, USP volume withdrawn.

Step 4: Withdraw the required volume from the reconstituted TEPEZZA vial(s) based on the patient's weight (in kg) and transfer into an intravenous bag containing 0.9% Sodium Chloride Solution, USP to prepare a diluted solution with a total volume of 100 mL (for less than 1800 mg dose) or 250 mL (for 1800 mg and greater dose). Mix diluted solution by gentle inversion. Do not shake.

The product does not contain any preservative. The combined storage time of reconstituted TEPEZZA solution in the vial and the diluted solution in the infusion bag containing 0.9% Sodium Chloride Injection, USP is a total of 4 hours at room temperature 20°C to 25°C (68°F to 77°F) or up to 48 hours under refrigerated conditions 2°C to 8°C (36°F to 46°F) protected from light. If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Upon reconstitution, TEPEZZA is a colorless

or slightly brown, clear to opalescent solution which is free of foreign particulate matter. Discard the solution if any particulate matter or discoloration are observed.

Do not freeze the reconstituted or diluted solution.

Discard vial(s) and all unused contents.

No incompatibilities between TEPEZZA and polyethylene (PE), polyvinyl chloride (PVC), polyurethane (PUR) or polyolefin (PO) bags and intravenous administration sets have been observed.

### **2.3 Administration**

Administer the diluted solution intravenously over 90 minutes for the first two infusions. If well tolerated, the minimum time for subsequent infusions can be reduced to 60 minutes. If not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes.

Do not administer as an intravenous push or bolus. TEPEZZA should not be infused concomitantly with other agents.

## **3 DOSAGE FORMS AND STRENGTHS**

For injection (intravenous infusion): 500 mg of teprotumumab as a white to off-white lyophilized powder in a single-dose vial for reconstitution and dilution.

## **4 CONTRAINDICATIONS**

None.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Infusion Reactions**

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

### **5.2 Exacerbation of Preexisting Inflammatory Bowel Disease**

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

### 5.3 Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two thirds of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

### 5.4 Hearing Impairment Including Hearing Loss

TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions [see *Warnings and Precautions (5.1)*]
- Exacerbation of Preexisting Inflammatory Bowel Disease [see *Warnings and Precautions (5.2)*]
- Hyperglycemia [see *Warnings and Precautions (5.3)*]
- Hearing Impairment Including Hearing Loss [see *Warnings and Precautions (5.4)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions ( $\geq 5\%$ ) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1. In addition, menstrual disorders (amenorrhea, metrorrhagia, dysmenorrhea) were reported in approximately 23% (5 of 22 patients) of menstruating women treated with TEPEZZA compared to 4% (1 of 25 patients) treated with placebo in the clinical trials.

**Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo**

<b>Adverse Reactions</b>	<b>TEPEZZA N=84 N (%)</b>	<b>Placebo N=86 N (%)</b>
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue <sup>a</sup>	10 (12%)	6 (7%)
Hyperglycemia <sup>b</sup>	8 (10%)	1 (1%)
Hearing impairment <sup>c</sup>	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0
Weight decreased	5 (6%)	0
Nail disorder <sup>d</sup>	4 (5%)	0

<sup>a</sup> Fatigue includes asthenia

<sup>b</sup> Hyperglycemia includes blood glucose increase

<sup>c</sup> Hearing impairment including hearing loss (deafness, including sensorineural deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, autophony and tinnitus)

<sup>d</sup> Nail disorder (includes nail discoloration, nail disorder and onychoclasia)

## 6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

## 6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEPEZZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Metabolism and Nutrition Disorders:* diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS)

*Otologic:* severe hearing impairment including hearing loss, which in some cases may be permanent

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor 1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss [see *Data*]. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA. If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

#### Data

##### *Animal Data*

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose (MRHD) based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternbrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.

### 8.3 Females and Males of Reproductive Potential

#### Contraception

##### *Females*

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

### 8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

### 8.5 Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

## 10 OVERDOSAGE

No information is available for patients who have received an overdose.

## 11 DESCRIPTION

Teprotumumab-trbw, an insulin-like growth factor-1 receptor inhibitor (IGF-1R), is a fully human IgG1 monoclonal antibody produced in Chinese hamster ovary (CHO-DG44) cells. It has a molecular weight of approximately 148 kilodaltons.

TEPEZZA (teprotumumab-trbw) for injection is supplied as a sterile, preservative-free, white to off-white, lyophilized powder for intravenous infusion. Each single-dose vial contains 500 mg of teprotumumab-trbw, L-histidine (7.45 mg), L-histidine hydrochloride monohydrate (31.8 mg), polysorbate 20 (1 mg), and trehalose dihydrate (946 mg). After reconstitution with 10 mL of Sterile Water for Injection, USP, the final concentration is 47.6 mg/mL with a pH of 5.5.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Teprotumumab-trbw's mechanism of action in patients with Thyroid Eye Disease has not been fully characterized. Teprotumumab-trbw binds to IGF-1R and blocks its activation and signaling.

### 12.2 Pharmacodynamics

No formal pharmacodynamic studies have been conducted with teprotumumab-trbw.

## 12.3 Pharmacokinetics

The pharmacokinetics of teprotumumab-trbw was described by a two compartment population PK model based on data from 40 patients with Thyroid Eye Disease receiving an initial intravenous infusion of 10 mg/kg, followed by infusions of 20 mg/kg TEPEZZA every 3 weeks in one clinical trial. Following this regimen, the mean ( $\pm$  standard deviation) estimates for steady-state area under the concentration curve (AUC), peak (C<sub>max</sub>), and trough (C<sub>trough</sub>) concentrations of teprotumumab-trbw were 138 ( $\pm$  34) mg•hr/mL, 632 ( $\pm$  139) mcg/mL, and 176 ( $\pm$  56) mcg/mL, respectively.

### Distribution

Following the recommended TEPEZZA dosing regimen, the population PK estimated mean ( $\pm$  standard deviation) for central and peripheral volume of distribution of teprotumumab-trbw were 3.26 ( $\pm$ 0.87) L and 4.32 ( $\pm$  0.67) L, respectively. The mean ( $\pm$  standard deviation) estimated inter-compartment clearance was 0.74 ( $\pm$  0.16) L/day.

### Elimination

Following the recommended TEPEZZA dosing regimen, the population PK estimated mean ( $\pm$  standard deviation) for the clearance of teprotumumab-trbw was 0.27 ( $\pm$  0.08) L/day and for the elimination half-life was 20 ( $\pm$  5) days.

### *Metabolism*

Metabolism of teprotumumab-trbw has not been fully characterized. However, teprotumumab-trbw is expected to undergo metabolism via proteolysis.

### Specific Populations

No clinically significant differences in the pharmacokinetics of teprotumumab-trbw were observed following administration of TEPEZZA based on patient's age (18-80 years), gender, race/ethnicity (103 White, 10 Black, and 3 Asian), weight (46-169 kg), mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min estimated by Cockcroft-Gault Equation), bilirubin levels (2.7-24.3 mcmol/L), aspartate aminotransferase (AST) levels (11-221 U/L), or alanine aminotransferase (ALT) levels (7-174 U/L). The effect of hepatic impairment on the pharmacokinetics of teprotumumab-trbw is unknown.

### Drug Interactions

No studies evaluating the drug interaction potential of TEPEZZA have been conducted.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

The carcinogenic potential of TEPEZZA has not been evaluated in long-term animal studies.

#### Mutagenesis

The genotoxic potential of TEPEZZA has not been evaluated.

Impairment of Fertility

Fertility studies have not been performed with TEPEZZA.

**14 CLINICAL STUDIES**

TEPEZZA was evaluated in 2 randomized, double-masked, placebo-controlled studies in 171 patients with Thyroid Eye Disease: Study 1 (NCT01868997) and Study 2 (NCT03298867). Patients were randomized to receive TEPEZZA or placebo in a 1:1 ratio. Patients were given intravenous infusions (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) every 3 weeks for a total of 8 infusions. Patients had a clinical diagnosis of Thyroid Eye Disease with symptoms and were euthyroid or had thyroxine and free triiodothyronine levels less than 50% above or below normal limits. Prior surgical treatment for Thyroid Eye Disease was not permitted. Proptosis ranged from 16 to 33 mm and 125 patients (73%) had diplopia at baseline.

A total of 84 patients were randomized to TEPEZZA and 87 patients were randomized to placebo. The median age was 52 years (range 20 to 79 years), 86% were White, 9% were Black or African-American, 4% were Asian and 1% identified as Other. The majority (73%) were female. At baseline, 27% of patients were smokers.

The proptosis responder rate at week 24 was defined as the percentage of patients with  $\geq 2$  mm reduction in proptosis in the study eye from baseline, without deterioration in the non-study eye ( $\geq 2$  mm increase) in proptosis. Additional evaluations included signs and symptoms of Thyroid Eye Disease including pain, gaze evoked orbital pain, swelling, eyelid erythema, redness, chemosis, inflammation, clinical activity score and assessments of functional vision and patient appearance. Results for proptosis are found in Table 2.

**Table 2. Efficacy Results in Patients with Thyroid Eye Disease in Study 1 and 2**

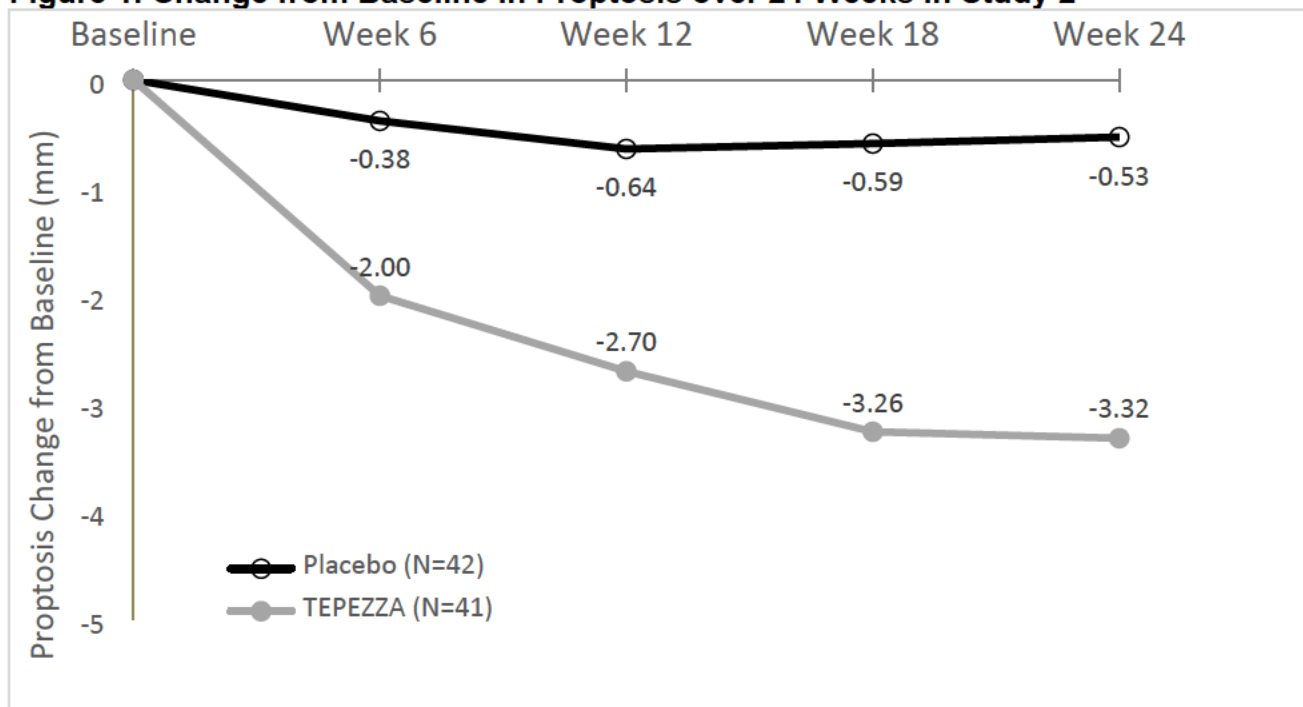
	Study 1			Study 2		
	Teprotumumab (N=42)	Placebo (N=45)	Difference (95% CI)	Teprotumumab (N=41)	Placebo (N=42)	Difference (95% CI)
Proptosis responder rate at week 24, % (n) <sup>1</sup>	71% (30)	20% (9)	51% (33, 69)	83% (34)	10% (4)	73% (59, 88)
Proptosis (mm) average change from baseline through week 24, LS Mean (SE) <sup>2</sup>	-2.5 (0.2)	-0.2 (0.2)	-2.3 (-2.8, -1.8)	-2.8 (0.2)	-0.5 (0.2)	-2.3 (-2.8, -1.8)

<sup>1</sup> Difference and its corresponding 95% Confidence Interval (CI) is based on a weighted average of the difference within each randomization stratum (tobacco user, tobacco non-use) using CMH weights.

<sup>2</sup> Results were obtained from an MMRM with an unstructured covariance matrix and including treatment, smoking status, baseline value, visit, treatment by visit, and visit by baseline value interaction as fixed effects. A change from Baseline of 0 was imputed at the first post-Baseline visit for any subject without a post-Baseline value.

In Study 2, improvement of proptosis as measured by mean change from Baseline was observed as early as 6 weeks and continued to improve through week 24 as shown in Figure 1. Similar results were seen in Study 1.

**Figure 1. Change from Baseline in Proptosis over 24 Weeks in Study 2**



TEPEZZA also led to improvement in the less severely impacted “fellow” eye.

Diplopia (double vision) was evaluated in a subgroup of patients that had diplopia at baseline in Study 1 and 2. Results are shown in Table 3.

**Table 3. Diplopia in Patients with Thyroid Eye Disease in Study 1 and 2**

Parameter	TEPEZZA (n=66)	Placebo (n=59)
Diplopia Responder rate <sup>a</sup> at week 24, % (n)	53% (35)	25% (15)

P<0.01

<sup>a</sup> Diplopia was evaluated on a 4-point scale where scores ranged from 0 for no diplopia to 3 for constant diplopia. A diplopia responder was defined as a patient with baseline diplopia >0 and a score of 0 at week 24.

Following discontinuation of treatment in Study 1, 53% of patients (16 of 30 patients) who were proptosis responders at week 24 maintained proptosis response 51 weeks after the last TEPEZZA infusion. 67% of patients (12 of 18) who were diplopia responders at week 24 maintained diplopia response 51 weeks after the last TEPEZZA infusion.

### Subgroups

Examination of age and gender subgroups did not identify differences in response to TEPEZZA among these subgroups. Reduction in proptosis was similar between smokers and non-smokers in both studies.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

TEPEZZA (teprotumumab-trbw) for injection is a sterile, preservative-free, white to off-white lyophilized powder available as follows:

Carton containing one 500 mg single-dose vial	NDC 75987-130-15
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Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton until time of use to protect from light. Do not freeze.

## **17 PATIENT COUNSELING INFORMATION**

### Embryo-Fetal Toxicity

- Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

### Infusion-related reactions

- Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

### Exacerbation of Preexisting Inflammatory Bowel Disease

- Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

### Hyperglycemia

- Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control measures including medications as appropriate. Encourage compliance with glycemic control.

### Hearing Impairment Including Hearing Loss

- Advise patients that TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Instruct patients to contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing.

BLA 761143/S-023

Page 14

Manufactured by:  
Horizon Therapeutics Ireland DAC  
Dublin, Ireland  
U.S. License No. 2022

Distributed by:  
Horizon Therapeutics USA, Inc.  
Deerfield, IL 60015

TEP-US-PI-006

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761143Orig1s023**

**OTHER REVIEW(S)**

Division of Ophthalmology Clinical/Labeling Review  
BLA 761143/S-023

<b>Product Title</b>	<b>TEPEZZA (teprotumumab-trbw) for injection, for intravenous use</b>
Applicant	Horizon Therapeutics Ireland DAC
Application Number	BLA 761143
Supplement Number	S-023
Supporting Document Number (SDN) Date FDA Received	SDN 929 July 7, 2023  SDN 920 June 21, 2023
Type of BLA Submission	351(a) Supplement
Approved Indication	Treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration
Pharmacologic Class	insulin-like growth factor-1 receptor inhibitor
Review Date	July 17, 2023
Reviewers	Derek Alberding, PharmD Clinical Analyst Division of Ophthalmology  Wiley A. Chambers, MD Director Division of Ophthalmology (DO)

**Summary:**

This review is an addendum to our clinical/labeling review signed in DARRTS on 5/11/2023. This Prior Approval labeling supplement, received 1/20/2023, proposed the following changes to the Prescribing Information (PI) for TEPEZZA:

1. Add a warning [REDACTED] (b) (4) in section 5 WARNINGS AND PRECAUTIONS.
2. Add "tinnitus" to the list of adverse reactions reported in the clinical trials in 6.1 Clinical Trials Experience.
3. Add "Otologic [REDACTED] (b) (4)" to the list of adverse reactions reported during postapproval use in 6.3 Postmarketing Experience.
4. Add "[REDACTED] (b) (4)" in 17 Patient Counseling Information.

**DO Clinical Comments:**

Agency-proposed PI was sent to Horizon Therapeutics (Horizon) via email on 5/11/2023. A video conference was held between representatives of Horizon and the FDA on 6/30/2023 to discuss the revised PI submitted on 6/21/2023.

The revised PI submitted on 7/7/2023 is acceptable. Horizon has addressed all of our recommendations and we have no additional comments at this time.

Division of Ophthalmology Clinical/Labeling Review  
BLA 761143/S-023

**Attachments:**

Attached to this review is the revised PI submitted on 7/7/2023. Agreed changes are presented in track changes.

**Recommendations:**

This Prior Approval labeling supplement is recommended for approval.

Derek Alberding, PharmD  
Clinical Analyst  
Division of Ophthalmology

Wiley A. Chambers, MD  
Director  
Division of Ophthalmology

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WILEY A CHAMBERS  
07/17/2023 12:50:39 PM

Division of Ophthalmology Clinical/Labeling Review  
BLA 761143/S-023

<b>Product Title</b>	<b>TEPEZZA (teprotumumab-trbw) for injection, for intravenous use</b>
Applicant	Horizon Therapeutics Ireland DAC
Application Number	BLA 761143
Supplement Number	S-023
Supporting Document Number (SDN) Date FDA Received	793 January 20, 2023
Supporting Document Number (SDN) Date FDA Received	810 February 15, 2023
Supporting Document Number (SDN) Date FDA Received	876 April 27, 2023
Type of BLA Submission	351(a) Supplement
Approved Indication	Treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration
Pharmacologic Class	insulin-like growth factor-1 receptor inhibitor
Review Date	May 10, 2023
Reviewers	Derek Alberding, PharmD Clinical Analyst Division of Ophthalmology  Wiley A. Chambers, MD Director Division of Ophthalmology (DO)

**Summary:**

This Prior Approval labeling supplement provides for the following changes to the Prescribing Information (PI) for TEPEZZA:

1. Add a warning [REDACTED] (b) (4) in section 5 WARNINGS AND PRECAUTIONS.
2. Add “tinnitus” to the list of adverse reactions reported in the clinical trials in 6.1 Clinical Trials Experience.
3. Add “*Otologic*: [REDACTED] (b) (4)” to the list of adverse reactions reported during postapproval use in 6.3 Postmarketing Experience.
4. Add [REDACTED] (b) (4) in 17 Patient Counseling Information.

**Background:**

The adverse reaction “hearing impairment (including deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)” was reported during the clinical trials for TEPEZZA.

Division of Ophthalmology Clinical/Labeling Review  
BLA 761143/S-023

During the *Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) Meeting* held on 12/13/2019, the episodes and frequency of reported hypoacusis/loss of hearing was discussed. The committee suggested that hearing loss be included in the WARNINGS AND PRECAUTIONS section of the product label since this side effect may affect a patient's decision to use teprotumumab, especially if the patient had prior hearing loss or has a family history of hearing loss. Please see the [transcript](#) for details of the committee discussion.

In the 1/21/2020 Approval letter, the applicant (Horizon) was required to conduct the following postmarketing requirement (PMR) according to the following schedule under 505(o):

PMR # 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: 8/2020  
First Patient Enrolled: 1/2021  
Study Completion: 5/2026  
Final Report Submission: 11/2026

This PMR includes a sub-study to evaluate potential hearing impairment.

On 1/26/2023, the Office of Surveillance and Epidemiology (OSE)/Division of Pharmacovigilance (DPV) opened a newly identified safety signal (NISS) (Safety Signal ID [SSID]# 1005044) (Standardized MedDRA Query [SQM] = *hearing loss*) based on medical literature case reports of sensorineural hearing loss with teprotumumab exposure. The Office of Pharmacovigilance and Epidemiology Integrated Review for NISS SSID# 1005044 was signed in DARRTS on 4/28/2022.

The Division of Ophthalmology disagreed with the OSE/DPV assessment that "hearing loss" is a newly identified safety signal with teprotumumab exposure. The NISS was opened over the objection of the Division.

**DO Clinical Comments:**

The Division of Ophthalmology disagrees with the labeling changes recommended in the 4/28/2022 OSE/DPV Integrated Review. The PMR hearing impairment sub-study (PMR # 3780-8) is ongoing and the final report is expected 11/2026.

In this supplement, Horizon submitted three case reports of the following adverse reactions following postapproval use of TEPEZZA:

- Permanent bilateral non-reversible hearing loss/ Permanent Neurosensory hearing loss due to nerve damage [Deafness neurosensory]
  - 44 year old female with no pre-existing hearing loss or impairment.
- Hearing loss/ bilateral moderate to severe sensorineural hearing loss [Deafness neurosensory]
  - 78 year old female with no pre-existing hearing loss or impairment. Hearing loss had not improved 8 months after completing therapy.
- Hearing loss [deafness]
  - 69 year old female with no pre-existing hearing loss. Treatment with TEPEZZA was discontinued prior to the 7<sup>th</sup> dose. Hearing loss was not resolved.

**5 WARNINGS AND PRECAUTIONS**

Horizon proposes to add the following new subsection:

**5.4** (b) (4)  
TEPEZZA may cause (b) (4).  
(b) (4)  
(b) (4) Assess patients' hearing (b) (4) with  
TEPEZZA and consider the benefit-risk of treatment with patients.

*DO Comment: We agree that listing a new warning for (b) (4) subsection 5.4 is appropriate.*

*We recommend clarifying in the subsection title (b) (4)*

*The three case reports describe hearing loss or hearing impairment that did not resolve following treatment completion or discontinuation. We recommend deleting the proposed terms (b) (4) and (b) (4). These terms are vague and not supported by the case reports.*

*The TEPEZZA hearing impairment sub-study (PMR # 3780-8) is currently ongoing. We have not identified factors that put patients at increased risk for hearing impairment or loss at this time, but agree that assessments of patient*

hearing are appropriate. We refer to the 4/28/2022 OSE/DPV Integrated Review and agree that including an assessment of hearing after treatment is appropriate.

We recommend revising the subsection 5.4 warning to read as follows:

**5.4 (b) (4) Hearing Impairment (b) (4) Hearing Loss**

TEPEZZA may cause (b) (4)

(b) (4) Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

## 6 ADVERSE REACTIONS

### *6.1 Clinical Trials Experience*

Horizon states that in the OPTIC-X open-label extension (OPTIC-X), 6 subjects experienced 7 events of hearing impairment (two of whom had also experienced events in the Phase 3 OPTIC trial). Two subjects experienced "tinnitus" during the OPTIC-X open-label extension.

***Reviewer Comment:*** Horizon proposes to add "tinnitus" to the definition of "hearing impairment" under **Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo.** Acceptable.

### *6.2 Postmarketing Experience*

Horizon proposes to add "Otologic: (b) (4)" to the list of adverse reactions reported during postapproval use.

***Reviewer Comment:*** We do not agree. These adverse reactions were observed in the clinical trials and should be listed in the Clinical Trials Experience subsection.

## 17 PATIENT COUNSELING INFORMATION

***Reviewer Comment:*** We recommend revising the proposed text for consistency with the description of hearing impairment and hearing loss in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections to read as follows:

**(b) (4) Hearing Impairment (b) (4) Hearing Loss**

Advise patients that TEPEZZA may cause severe hearing impairment (b) (4) (b) (4). Instruct patients to contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing.

Division of Ophthalmology Clinical/Labeling Review  
BLA 761143/S-023

Our recommendations to add a warning for the risk of hearing impairment and hearing loss in the PI are summarized below:

<b>HIGHLIGHTS</b>	
Applicant Proposed Text (in red font)	DO Proposed Revisions (in red font)
(b) (4)	<p style="text-align: center;">-----<b>WARNINGS AND PRECAUTIONS</b>-----</p> <ul style="list-style-type: none"> <li>• <b>Infusion Reactions:</b> If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management (5.1)</li> <li>• <b>Exacerbation of Preexisting Inflammatory Bowel Disease (IBD):</b> Monitor patients with preexisting IBD for flare of disease; discontinue TEPEZZA if IBD worsens (5.2)</li> <li>• <b>Hyperglycemia:</b> Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving TEPEZZA (5.3)</li> <li>• (b) (4) <b>Hearing Impairment</b> (b) (4) <b>Hearing Loss:</b> TEPEZZA may cause (b) (4) (b) (4). Assess patients' hearing before, (b) (4) during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients (5.4)</li> </ul>
<b>FULL PRESCRIBING INFORMATION</b>	
Applicant Proposed Text (in red font)	DO Proposed Revisions (in red font)
(b) (4)	<p><b>5 WARNINGS AND PRECAUTIONS</b></p> <p>5.4 (b) (4) <b>Hearing Impairment</b> (b) (4) <b>Hearing Loss</b></p> <p>TEPEZZA may cause (b) (4)</p> <p style="background-color: #cccccc; height: 20px; margin: 5px 0;"></p> <p style="background-color: #cccccc; height: 20px; margin: 5px 0;"></p> <p style="background-color: #cccccc; height: 20px; margin: 5px 0;"></p> <p>Assess patients' hearing before, (b) (4) -during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.</p>

(b) (4)

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions [see *Warnings and Precautions (5.1)*]
- Exacerbation of Preexisting Inflammatory Bowel Disease [see *Warnings and Precautions (5.2)*]
- Hyperglycemia [see *Warnings and Precautions (5.3)*]
- Hearing Impairment (b) (4) **Hearing Loss** [see *Warnings and Precautions (5.4)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions ( $\geq 5\%$ ) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

In addition, menstrual disorders (amenorrhea, metrorrhagia, dysmenorrhea) were reported in approximately 23% (5 of 22 patients) of menstruating women treated with TEPEZZA compared to 4% (1 of 25 patients) treated with placebo in the clinical trials.

(b) (4)

**Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo**

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue <sup>a</sup>	10 (12%)	6 (7%)
Hyperglycemia <sup>b</sup>	8 (10%)	1 (1%)
Hearing impairment <sup>c</sup>	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0
Weight decreased	5 (6%)	0
Nail disorder <sup>d</sup>	4 (5%)	0

<sup>a</sup> Fatigue includes asthenia

<sup>b</sup> Hyperglycemia includes blood glucose increase

<sup>c</sup> Hearing impairment <sup>(b) (4)</sup> **hearing loss** (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, autophony and tinnitus)

<sup>d</sup> Nail disorder (includes nail discoloration, nail disorder and onychoclasia)

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEPEZZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Metabolism and Nutrition Disorders:* diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS).

*Otologic:* <sup>(b) (4)</sup>

### 17 PATIENT COUNSELING INFORMATION

<sup>(b) (4)</sup> **Hearing Impairment** <sup>(b) (4)</sup> **Hearing Loss**

Advise patients that TEPEZZA may cause

<sup>(b) (4)</sup> **severe** hearing impairment <sup>(b) (4)</sup>

**Instruct** patients <sup>(b) (4)</sup> **to** contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing.

Division of Ophthalmology Clinical/Labeling Review  
BLA 761143/S-023

**DO Labeling Comments:**

Prescribing Information

1. In Highlights, delete the “Warnings and Precautions, Hyperglycemia (5.3)” listing under Recent Major Changes. A changed section must be listed under this heading in HL for at least one year after the date of the labeling change and must be removed at the first printing after the one year period.

Container Label and Carton Labeling

Revised container labels and carton labeling were not included in this submission.

**Attachments:**

Attached to this review is the revised PI submitted on 4/27/2023. DO labeling recommendations are presented in **highlighted** track changes.

**Recommendations:**

This Prior Approval labeling supplement is not recommended for approval. The attached Agency-proposed labeling should be shared with the applicant.

Derek Alberding, PharmD  
Clinical Analyst  
Division of Ophthalmology

Wiley A. Chambers, MD  
Director  
Division of Ophthalmology

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DEREK S ALBERDING  
05/10/2023 04:24:12 PM

WILEY A CHAMBERS  
05/11/2023 09:52:42 AM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761143Orig1s023**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



BLA 761143

**NOTIFICATION OF  
NEWLY IDENTIFIED SAFETY SIGNAL**

Horizon Therapeutics Ireland DAC  
c/o Horizon Therapeutics USA Inc  
Attention: Fred Henry, MS, MPH  
Senior Director, Regulatory Affairs  
1 Horizon Way  
Deerfield, IL 60015

Dear Mr. Henry:

FDA staff in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) regularly conduct routine safety surveillance. When a safety signal for a marketed drug or biologic product is identified (from various sources, such as our FDA Adverse Event Reporting System (FAERS) database, literature, or regulatory submissions), a Newly Identified Safety Signal (NISS) is created in CDER's Lifecycle Signal Tracker (LiST) to facilitate timely evaluation and management.

A NISS evaluation began on January 26, 2023, for your product, TEPEZZA (teprotumumab-trbw) for injection, regarding hearing impairment. This NISS has been classified as an important potential risk.

As you may know, Title IX, Section 921 of the Food and Drug Administration Amendments Act 2007 (FDAAA) (121 Stat. 962) amends the Federal Food, Drug and Cosmetic Act (FDCA) to add a new subsection (k)(5) to section 505 (21 U.S.C. 355). This section in FDAAA, among other things, directs FDA to "post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by the Adverse Event Reporting System within the last quarter."

To comply with Section 921 of FDAAA, the Agency reviews the LiST database for all NISS that were identified for evaluation each quarter, and those that are based wholly or in part on FAERS data are posted in the corresponding quarter on the FAERS web site. Because your safety issue is based in part on FAERS data, it will be included in the first quarter posting for 2023. Additional information on Section 921 and the quarterly reports are available at FDA.gov.<sup>1</sup>

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<sup>1</sup> <https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system>

If you have any questions, call me at (240) 402-0963.

Sincerely,

*{See appended electronic signature page}*

Derek Alberding, PharmD  
Clinical Analyst  
Division of Ophthalmology  
Office of Specialty Medicine  
Center for Drug Evaluation and Research

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DEREK S ALBERDING  
06/02/2023 02:18:33 PM

June 2, 2023

second quarter posting” should state “first quarter posting”. The letter was not sent to the sponsor/applicant. Refer to the corrected letter dated 6/2/2023.



BLA 761143

**NOTIFICATION OF  
NEWLY IDENTIFIED SAFETY SIGNAL**

Horizon Therapeutics Ireland DAC  
c/o Horizon Therapeutics USA Inc  
Attention: Fred Henry, MS, MPH  
Senior Director, Regulatory Affairs  
1 Horizon Way  
Deerfield, IL 60015

Dear Mr. Henry:

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To comply with Section 921 of FDAAA, the Agency reviews the LiST database for all NISS that were identified for evaluation each quarter, and those that are based wholly or in part on FAERS data are posted in the corresponding quarter on the FAERS web site. Because your safety issue is based in part on FAERS data, it will be included in the second quarter posting for 2023. Additional information on Section 921 and the quarterly reports are available at FDA.gov.<sup>1</sup>

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<sup>1</sup> <https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system>

If you have any questions, call me at (240) 402-0963.

Sincerely,

*{See appended electronic signature page}*

Derek Alberding, PharmD  
Clinical Analyst  
Division of Ophthalmology  
Office of Specialty Medicine  
Center for Drug Evaluation and Research

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BLA 761143/S-023

**ACKNOWLEDGMENT --  
PRIOR APPROVAL SUPPLEMENT**

Horizon Therapeutics Ireland DAC  
c/o Horizon Therapeutics, USA, Inc.  
Attention: Fred Henry, MS, MPH  
Senior Director Regulatory Affairs  
1 Horizon Way  
Deerfield, IL 60015

Dear Mr. Henry:

We have received your supplemental biologics license application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

**BLA NUMBER:** 761143  
**SUPPLEMENT NUMBER:** 023  
**PRODUCT NAME:** TEPEZZA (teprotumumab-trbw) for injection  
**DATE OF SUBMISSION:** January 20, 2023  
**DATE OF RECEIPT:** January 20, 2023

This supplemental application proposes additions to the WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS sections of the Prescribing Information. Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 21, 2023, in accordance with 21 CFR 601.2(a). If the application is filed, the goal date will be July 20, 2023.

If you have questions about this supplement, call me at (240) 402-0963.

Sincerely,

*{See appended electronic signature page}*

Derek Alberding, PharmD  
Clinical Analyst  
Division of Ophthalmology  
Office of Specialty Medicine  
Center for Drug Evaluation and Research

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