CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761143Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	January 14, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Eric Hales, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1 (DBBR 1)
Application:	BLA 761143
Applicant:	Horizon Therapeutics Ireland DAC
Submission Date:	July 8, 2019
Product:	Teprotumumab-trbw
Dosage form(s):	For injection
Strength and Container-Closure:	500 mg/vial in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The container label submitted on December 13, 2019 and the prescribing information provided via email by DTOP clinical team on January 13, 2020 meet regulatory requirements for labeling and are acceptable from an OBP labeling perspective. The carton labeling provided via email by DTOP PM dated January 10, 2020 does not meet 21 CFR 201.100(b)(5) and therefore is unacceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

Many aspects of this assessment are incomplete and recommended labeling revisions were not implemented due to recommendations not being sent to the applicant by DTOP. OBP labeling was unable to confirm absence of text (b) (4) for the vial and unable to confirm that sufficient area of the container for visual inspection. OBP labeling was unable to confirm that the carton labeling has the quantitative information of the inactive ingredients, thus, the carton labeling provided via email by DTOP PM dated January 10, 2020 does not meet the regulatory requirement per 21 CFR 201.100(b)(5) and is unacceptable.

CONCLUSION

The container label submitted on December 13, 2019 and the prescribing information provided via email by DTOP clinical team on January 13, 2020 meet regulatory requirements for labeling and are acceptable from an OBP labeling perspective.

The carton labeling provided via email by DTOP PM dated January 10, 2020 does not meet 21 CFR 201.100(b)(5) and therefore is unacceptable from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling
Prescribing Information (submitted on July 8, 2019 \\cdsesub1\evsprod\bla761143\0001\m1\us\11413-proposed-pi-word.docx)
Medication Guide (submitted on July 8, 2019 \\cdsesub1\evsprod\bla761143\0001\m1\us\11413-proposed-med-guide-word.docx)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	☐ Yes ☐ No ☒ N/A
Recommended labeling practices (U.S license number for container bearing a partial label)	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial label

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

(b) (4) *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: Confirm there is no text on (b) (4) the vials.
Per email dated January 13, 2020, DTOP informed OBP labeling that DTOP disagreed with the necessity of the request made by OBP labeling to confirm absence of tex (b) (4) (b) (4) *This request was not sent to the applicant by DTOP. Per United States Pharmacopeia (USP) General Chapters: <7> Labeling: Products that do not require cautionary statements should be free of information, so that those with cautionary statements are immediately apparent. Accomplishing this requires a systematic approach to*

the labeling of injectable products, and one that ensures that (b) (4) *an area of these products that is highly visible to practitioners as they use these medicines—is reserved for critical safety messages. OBP labeling has determined that this is unacceptable but acknowledges that this is not a regulatory requirement.*

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located

Per email dated January 13, 2020, DTOP informed OBP labeling that DTOP disagreed with the necessity of the request made by OBP labeling to confirm that sufficient area of the container for visual inspection. This request was not sent to the applicant by DTOP. OBP labeling is unable to determine that this regulatory requirement has been met and has determined that this is unacceptable.

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

***NDC numbers* (container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors,	☐ Yes ☐ No

April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☒ N/A

Comment/Recommendation: partial label

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No

	☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that a linear barcode appears on the container label. *The Applicant revised as requested*

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial label

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial label

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[5] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that the lot number appears on the carton labeling
The Applicant revised as requested

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that the expiration date appears on the carton labeling. *The Applicant revised as requested*

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	☐ Yes ☐ No ☒ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider revising storage statement as follows: **"Storage:** 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."
Per email dated January 13, 2020, DTOP informed OBP labeling that DTOP disagreed with the necessity of the recommendation made by OBP labeling to revise the storage information. This recommendation was not implemented because this proposed revision was not sent to the applicant by DTOP.

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	☐ Yes ☒ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	☐ Yes ☒ No ☐ N/A

Comment/Recommendation: Revise the contents list to include the quantitative information of the inactive ingredients (added per 3.2.P.1 submission) as follows: "Each single-dose vial delivers 500 mg of teprotumumab-trbw, L-histidine (7.45 mg), L-histidine hydrochloride monohydrate (31.8 mg), polysorbate 20 (1 mg), and α, α-trehalose dihydrate (946 mg)."
Per email dated January 13, 2020, DTOP informed OBP labeling that DTOP disagreed with the necessity of this request made by OBP labeling. This recommendation was not implemented because this proposed revision was not sent to the applicant by DTOP. OBP labeling has determined that this does not meet the regulatory requirement per 21 CFR 201.100(b)(5) and therefore is unacceptable.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	✓ Yes ☐ No ☐ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider revising the Statement of Dosage from "See enclosed package insert for reconstitution instructions and complete information on dosage and administration" to read "Dosage: See Prescribing Information"
Per email dated January 13, 2020, DTOP informed OBP labeling that DTOP disagreed with the necessity of this request made by OBP labeling. This recommendation was not implemented because this proposed revision was not sent to the applicant by DTOP.

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The Medication Guide statement shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. Ensure that the carton labeling has the following statement: "ATTENTION: Dispense the enclosed Medication Guide to Each Patient" or "Always Dispense enclosed Medication Guide to Each Patient"
Per email dated January 13, 2020, DTOP informed OBP labeling that this product will not have a Medication Guide.

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Added the color and clarity of the reconstituted solution per 3.2.P.1 submission
The applicant revised as requested

Revised to USP nomenclature from (b) (4) to "0.9% Sodium Chloride Injection, USP"
The applicant revised as requested

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	☐ Yes ☒ No ☐ N/A

Comment/Recommendation:
The pharmacological class was added per 21 CFR 201.57(c)(12)
The applicant revised as requested

Added the cell line "Chinese hamster ovary cell line (CHO-DG44)"

The applicant revised as requested

Added the quantitative information of the inactive ingredients per 3.2.P.1 submission as follows: "Each single-dose vial delivers 500 mg of teprotumumab-xxxx, L-histidine (7.45 mg), L-histidine hydrochloride monohydrate (31.8 mg), polysorbate 20 (1 mg), and α, α-trehalose dihydrate (946 mg)."
The applicant revised as requested

Consider adding the reconstitution information as follows: "After reconstitution with 10 mL of Sterile Water for Injection, USP, the final concentration is 50 mg/mL with a pH of 5.5"

The applicant revised but they determined that the final concentration is 47.6 mg/mL, however, the resultant concentration was removed from sections 2 and 11 of the PI in the January 9th version of the prescribing information provided by DTOP PM January 10th to OBP labeling. In an email dated January 13th, OBP labeling was provided a different version of the prescribing information by DTOP clinical team that included the resultant concentration in section 11 only and OBP labeling requested removal of the resultant concentration sentence from section 11 for consistency with section 2 and to prevent dosing confusion. OBP labeling is unable to determine that this revision will be made since the version of the PI provided to OBP labeling, as of January 14, 2020, does not included this revision. This is unacceptable.

Full Prescribing Information	
15 Cytotoxic Drug reference	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures.1 1.OSHA Hazardous Drugs. OSHA. [Accessed on June 9, 2017, from http://www.osha.gov/SLTC/hazardousdrugs/index.html	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The dosage form was added per 21 CFR 201.57(c)(17)
The applicant revised as requested

Revised storage statement as follows: "Refrigerate at 36°F to 46°F (2°C to 8°C) in original carton until time of use to protect from light. Do not freeze." *The applicant revised as requested*

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Relocated the US license number to appear with the manufacturer *The applicant revised as requested*

Medication Guide Evaluation (N/A)
Patient Information Labeling Evaluation (N/A)
Instructions for Use Evaluation (N/A)

11 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 1/14/2020 02:52:19PM
GUID: 50814c7000007a3d59329f660d8ddf02

Eric Hales

Digitally signed by Eric Hales
Date: 1/14/2020 03:02:06PM
GUID: 57d6a5ef01b1162fe9ae3a025d49565e

First Approval for Indication/Breakthrough Review/Priority Review

Recommendation:
BLA 761143: Approval

BLA Number: 761143
Review
Review Date: 12/16/2019

Drug Name/Dosage Form	teprotumumab-trbw (trade name pending)/injection
Strength/Potency	500 mg/vial (50 mg/mL)
Route of Administration	intravenous infusion
Rx/OTC dispensed	Rx
Indication	Insulin-like growth factor-1 receptor inhibitor for the treatment of Thyroid Eye Disease
Applicant/Sponsor	Horizon Therapeutics Ireland DAC
US agent, if applicable	Horizon Pharma USA Inc.

Product Overview:

Teprotumumab-trbw is a recombinant, human IgG1κ monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells. Teprotumumab-trbw binds to the alpha-subunit of the insulin-like growth factor-1 receptor (IFG-1R) and inhibits the ligand-receptor binding interaction between IGF-1 and IGF-2 with IGF-1R. This inhibition leads to the inhibition of autophosphorylation of IGF-1R and prevention of the activation of downstream signaling pathways that promote cell proliferation and facilitates downregulation of IGF-1R expression through lysosomal internalization and receptor degradation.

Teprotumumab-trbw drug substance (DS) is (b) (4).
Teprotumumab-trbw drug product (DP) is supplied at 500 mg/vial as a sterile, lyophilized powder for intravenous infusion. Upon reconstitution with 10 (b) (4) ml of sterile water for injection, the reconstituted protein concentration of teprotumumab-trbw DP is 50 mg/ml. Teprotumumab-trbw is indicated for the treatment of Thyroid Eye Disease (TED).

Quality Review Team:

Discipline	Reviewer	Branch/Division
Drug Substance/Drug Product	Eric Hales	DBRRI/OBP/OPQ
Immunogenicity/Analytical Method Validation	Chia-Wen Hsu	DBRRI/OBP/OPQ
Labeling	Vicky Borders-Hemphill	DBRRI/OBP/OPQ
Facility	Ashley Queen/Zhong Li/Thuy Thanh Nguyen (TL)	DBM/OPMA/OPQ
Microbiology	Reyes Candauchacon/Bo Chi/Jessica Hankins (QAL)	DBM/OPMA/OPQ
Application Team Lead	Kristen Nickens	DBRRI/OBP/OPQ
Tertiary Reviewer for OBP	Qing (Joanna) Zhou	DBRRI/OBP/OPQ
Business Project Manager	Anh-Thy Ly	RBPMBI/OPRO/OPQ

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Jacquelyn Smith	CDER/OND/OAP/DTOP
Cross-disciplinary Team Lead	William Boyd	CDER/OND/OAP/DTOP
Medical Officer	Wiley Chambers	CDER/OND/OAP/DTOP
Pharmacology/Toxicology	Andrew McDougal/Lori Kotch	CDER/OND/OAP/DTOP
Clinical Pharmacology	Abhay Joshi/Philip Colangelo	CDER/OTS/OCP/DCPIV
Statistics	Yunfan Deng/Yan Wang	CDER/OTS/OB/DBIV

1. Names:
   a. Proprietary Name: Pending ("Tepezza" and (b) (4) under review)
   b. Trade Name: Pending ("Tepezza" and (b) (4) under review)
   c. Non-Proprietary Name/USAN: teprotumumab-trbw
   d. CAS Name: 89957-37-9
   e. Common Name: HZN-001
   f. INN Name: teprotumumab-trbw
   g. Compendial Name: N/A
   h. OBP systematic name: MAB HUMAN (IGG1) ANTI P08069 (IGF1R_HUMAN) [HZN001]

Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request #1	July 22, 2019
Information Request #2	August 9, 2019
OND Filing Meeting	August 19, 2019
Filing Letter	August 28, 2019
Filing Memo	August 30, 2019
Information Request #3	October 1, 2019
Information Request #4	October 4, 2019
Information Request #5	October 8, 2019
Information Request #6	October 23, 2019
OND Mid-Cycle Meeting	October 23, 2019
Information Request #7	November 4, 2019
Mid-Cycle Communication with Sponsor	November 6, 2019
CMC -Sponsor Teleconference 1	November 8, 2019
Information Request #8	November 8, 2019
OND Pre-Late Cycle Meeting	November 20, 2019
Information Request #9	November 21, 2019
Information Request #10	November 20, 2019
Information Request #11	November 27, 2019
OND Wrap Up Meeting	December 2, 2019
Information Request #12	December 3, 2019
Labeling Meeting	December 4, 2019
Late-Cycle Meeting with Sponsor	December 4, 2019
Information Request #13	December 10, 2019
CMC – Sponsor Teleconference 2	December 12, 2019

DODAC Meeting	December 13, 2019

Submissions Reviewed (OPQ):

Submission:	Date Received:	Review Completed (Yes/No)
STN 0001/1	July 8, 2019	Yes (OBP/OPMA)
STN 0002/2 (response to IR#1)	July 24, 2019	Yes (OPMA)
STN 0003/3 (stability update)	July 26, 2019	Yes (OBP)
STN 0004/4 (response to IR#2)	August 14, 2019	Yes (OBP/OPMA)
STN 0010/10 (response to IR#3)	October 9, 2019	Yes (OPMA)
STN 0011/11 (response to IR#4)	October 16, 2019	Yes (OBP)
STN 0012/12 and STN 0018/18 (response to IR#5)	October 17 and November 7, 2019	Yes (OPMA)
STN 0014/14 (Sponsor update to BLA)	October 28, 2019	Yes (OBP)
STN 0016/16, STN 0017/17, and STN 0031/31 (response to IR#6)	November 5 and 6, 2019	Yes (OBP/OPMA)
STN 0019/19, STN0021/21, STN 0022/22, and STN 0026/26 (response to IR#7)	November 12, 14, and 22, 2019	Yes (OBP)
STN 0023/23 (response to IR#8)	November 15, 2019	Yes (OPMA)
STN 0025/25, STN 0027/27 and STN 0031/31 (response to IR#9)	November 22 and 25, 2019	Yes (OBP/OPMA)
STN 0026/26 (response to IR#10)	November 22, 2019	Yes (OBP/OPMA)
STN 0029/29 (response to IR#11)	December 3, 2019	Yes (OPMA)
STN 0030/30 (Response to IR#12)	December 9, 2019	Yes (OBP)
SDN 32 (Response to IR#12 and IR#13)	December 16, 2019	Yes (OBP)

Quality Review Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Comments
(b) (4)	III		(b) (4)	2	Adequate	
	V			3, 6	Adequate	6- Inspection of the facility was performed to support licensure
	III			3	Adequate	
	V			2	Adequate	
	V			2	Adequate	
	III			3	Adequate	

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under “comments”)

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

   B. Other documents: IND 112952

3. Consults: None

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761143 for teprotumumab-trbw manufactured by Horizon Therapeutics Ireland, DAC. The data submitted in this application are adequate to support the conclusion that the manufacture of teprotumumab-trbw is well-controlled and leads to a product that is safe, pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

C. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: (b) (4) (b) (4)
  - Drug Product: (b) (4) (b) (4)
- Fill size and dosage form: 500 mg single-dose vial for injection
- Dating period:
  - Drug Product: 18 months: 5±10°C
  - Drug Substance: (b) (4)
  - For packaged products: “Not packaged”
  - Stability Option:
    - For stability protocols:
      - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release:
  - Yes
  - Rationale: specified product in accordance with 21 CFR 601.2a
    Note: teprotumumab-trbw is exempted from lot release per FR 95-29960.

D. Benefit/Risk Considerations: Teprotumumab-trbw is indicated for the treatment of Thyroid Eye Disease (TED), also known as thyroid-associated ophthalmopathy, Graves’ ophthalmopathy or Graves’ orbitopathy. TED is a rare autoimmune disease most commonly associated with Graves’ hyperthyroidism, that is associated with comorbidities such as debilitating orbital pain, periorbital inflammation, eyelid retraction, proptosis (eye protrusion; occurring in ~62% of patients), compromised eye motility, dysthyroid optic neuropathy, facial disfigurement and blindness. Proptosis was the primary endpoint for the clinical evaluation of

teprotumumab-trbw. TED presents in an active phase (associated with visible signs of inflammation) associated with progressive severity, followed by an inactive phase (absent of inflammation but with significant orbital tissue remodeling) where no additional deterioration occurs, but the comorbidities persist. Therefore, efficacious patient treatment options are desirable within the active treatment window (~1-3 years). There are currently no US-based treatment guidelines for active TED; however, the most common options include the use of corticosteroids, orbital irradiation, and orbital surgery. The use of corticosteroids provides a short-term reduction of inflammation, with minimal effect on proptosis. Orbital irradiation is less commonly used in the US, except for patients that are intolerant or have contraindications to the use of corticosteroids. Orbital surgery is commonly used to repair the outcomes associated with TED once the active phase subsides. Further, no treatments have been shown effective for proptosis, which is secondary to the inflammation (activation of orbital fibroblasts) and cellular proliferation. The inflammation and cellular proliferation are associated with activation of IGF-1R by its endogenous ligands (IGF-1 and IGF-2), autophosphorylation of tyrosine residues in the cytoplasmic β-subunit, and downstream signal activation of proliferative pathways. IGF-1R is upregulated in orbital fibroblasts, T-cells, and B-cells in TED patients. Therefore, inhibition of IGF-1R signaling by teprotumumab, which selectivity binds to the extracellular α-subunit of IGF-1R, blocks inflammatory responses that contribute to disease progression in TED patients, such as constitutive activation of the receptor and downstream signal transduction pathways that promote cell proliferation and inflammation.

The overall control strategy for teprotumumab-trbw manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with (b) (4) controls, process monitoring tests, release testing, and stability testing ensures overall process consistency that results in DS and DP with appropriate quality and free of adventitious agents.

B. Recommendation on Phase 4-Draft (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

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.

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.

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.

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.

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.

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.

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

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
IGF-1R binding (potency)	Efficacy	Intrinsic to the molecule. (b) (4)	(b) (4)	
		Minimal change is expected during storage through expiry.		The current IGF-1R potency assay is a commercially-sourced kit. The sponsor is asked in a PMC to establish an in-house qualification program to ensure consistency and control over the commercial kit, and to ultimately develop an in-house cell-based assay to control the potency of

				teprotumumab-trbw. The sponsor is asked in a PMC to revalidate the IGF-1R AlphaLISA potency assay to ensure proper implementation of the internal potency assay control.
Identity	Safety and Efficacy	Intrinsic to the molecule	(b) (4)	
High Molecular Weight (HMW) species/Aggregates (product-related impurities)	Efficacy (impacts IGF-1R binding), Safety/Immunogenicity and PK	Manufacturing process (b) (4) (b) (4) Minimal change is expected during storage under recommended conditions through expiry.	(b) (4)	N/A
Fragments (LMW species)	Efficacy and PK	Manufacturing process, (b) (4) (b) (4) Minimal increase in fragments is expected during storage under recommended conditions.		N/A

			Impact on potency is also controlled through potency testing.	
Oxidation (b) (4) (b) (4)	Efficacy and PK	Manufacturing process (b) (4) (b) (4) Minimal change is expected on stability.	(b) (4)	N/A
Deamidation	PK	Manufacturing process (b) (4) (b) (4) Minimal change is expected on stability.		N/A
Succinimide intermediate/Isomerization	Efficacy and PK	Manufacturing process, (b) (4) (b) (4) Minimal change is expected on stability.		N/A
(b) (4)	N/A	Manufacturing process (b) (4) Minimal change is expected on stability.		N/A
Osmolality	Safety and Efficacy (control of degradation through formulation)	Formulation		N/A
pH	Safety and Efficacy	Formulation (b) (4)		N/A

			(b) (4)	
Protein content	Efficacy	Manufacturing process		N/A
Polysorbate 20 (PS 20)	Safety	Formulation		N/A

B. Drug Substance [teprotumumab-trbw] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management. (see example in Attachment 2)

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Host Cell Proteins (HCP) (Process-related impurity)	Safety and Immunogenicity	Production cell line		(b) (4) (b) (4) The sponsor is asked to develop and validate a product-specific HCP assay with improved sensitivity in a PMC.
Host Cell DNA (Process-related impurity)	Safety	Production cell line		N/A
(b) (4) (Process-related impurity)	Safety and Immunogenicity	Process-related impurity (b) (4) (b) (4)		N/A

			(b) (4)	
(b) (4) (Process-related impurity)	Safety	Process-related impurity (b) (4) (b) (4)		N/A
(b) (4) (Process-related impurity)	Safety, immunogenicity	(b) (4)		N/A
(b) (4) (Process-related impurity)	Safety	(b) (4)		N/A
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations		N/A

			(b) (4)	
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations.		N/A
Leachables (Process-related impurity)	Safety	Manufacturing components and the DS container closure system		N/A
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process		N/A
Endotoxin	Safety and purity	Endotoxin can be introduced by raw materials and contamination during manufacturing		N/A

- Description: Teprotumumab-trbw is a recombinant, human IgG1κ monoclonal antibody manufactured in Chinese Hamster Ovary (CHO) cells. (b) (4) (b) (4) (b) (4). The intact molecular weight of teprotumumab is 148 kDa.

  The protein concentration of teprotumumab-trbw is measured using UV-spectrophotometry (b) (4) and the theoretical extinction coefficient, (b) (4)

The experimental extinction coefficient is (b) (4) The theoretical extinction coefficient was used during clinical development and will continue to be used to determine teprotumumab protein concentration for commercial use.

- Mechanism of Action (MoA): Teprotumumab-trbw is a human IgG1 monoclonal antibody that selectively binds to the extracellular α-subunit of IGF-1R but does not bind to insulin receptor or impact insulin binding. Teprotumumab-trbw inhibits IGF-1 and IFG-2 from binding to IGF-1R, thereby preventing the autophosphorylation and activation of downstream signal transduction pathways that promote cellular proliferation and facilitates downregulation of IGF-1R through internalization and degradation. Teprotumumab-trbw does not demonstrate antibody-dependent cellular cytotoxicity (ADCC) or compliment-dependent cytotoxicity (CDC).

- Potency Assay: A commercial AlphaLISA cell-based assay kit, that measures the downstream phosphorylation of the IGF-1R signaling pathway is utilized to determine the potency of teprotumumab-trbw. IGF-1R phosphorylation is measured by luminescent bead excitation, and phosphorylation is inversely correlated with the teprotumumab-trbw inhibition of IGF-1R signaling. Relative potency is reported as a percent of reference standard activity. An internal potency assay quality control is implemented to monitor the performance of the potency assay and reference standard stability.

- Reference Materials: Teprotumumab-trbw utilizes (b) (4)
(b) (4)

- Critical starting materials or intermediates: The production cell line for teprotumumab-trbw was derived from CHO-DG44 cells, (b) (4)
(b) (4)
(b) (4). A two-tiered cell banking system consisting of a Master Cell Bank (MCB) and a Working Cell Bank (WCB) was implemented to ensure continued source for production. Viability of both the MCB and WCB is monitored as part of a stability program. Adequate testing for adventitious agents was performed.

  Manufacturing process summary: Teprotumumab-trbw DS is manufactured (b) (4)
(b) (4)

(b) (4)

- Container closure: The DS is stored (b) (4) (b) (4). The container closure system is suitable for teprotumumab-trbw DS, based on stability data and maintenance of closure integrity.

- Dating period and storage conditions: The dating period for the DS is (b) (4) when stored at (b) (4).

C. Drug Product [teprotumumab-trbw] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for DP CQAs that derive from the DP manufacturing process and general DP attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance – lyophilized product	Safety and Efficacy (stability)	Manufacturing process	(b) (4)	N/A
Appearance – reconstituted product	Safety and Efficacy (stability)	Manufacturing process		N/A
Color and opalescence solution (general)	Safety and Efficacy	Formulation, contamination, or degradation		N/A
(b) (4)	Efficacy (stability)	Manufacturing Process		N/A

Reconstitution time	Efficacy/Dosing	Manufacturing process	(b) (4)	N/A
Extractable volume	Efficacy/Dosing	Manufacturing process		N/A
Deliverable Content (general)	Efficacy/Dosing	Manufacturing process		N/A
Particulate Matter (visible and subvisible) (Product or Process Related Impurities)	Safety/ Immunogenicity	Manufacturing process and container closure system		N/A
Leachables (process-related impurities)	Safety	Manufacturing equipment and container closure		A leachables study under accelerated conditions was performed (b) (4) (b) (4). The sponsor will be asked to provide the final study report for leachable evaluation for the DP under long-term storage conditions throughout the product shelf-life in a PMC.
Sterility (Contaminant)	Safety risk to patients (infection) Efficacy (degradation or modification of the product by microorganisms or their byproducts)	Contaminants could be introduced throughout DP manufacturing		The sponsor is asked in a PMC to validate the (b) (4) teprotumumab drug product (b) (4) (b) (4) (b) (4)
Endotoxin (Contaminant)	Safety, purity, and immunogenicity	Contaminants could be introduced throughout DP manufacturing process and through raw materials		N/A
Container Closure Integrity (Sterility Assurance)	Safety (loss of sterility due to breaches in Container Closure Integrity) or evaporation/leakage	Container closure breaches during drug product shelf-life.		N/A

	(impacting concentration or content)			

- Potency and Strength: Teprotumumab-trbw is supplied at 500 mg/vial. Potency is defined as the percent activity relative to the current teprotumumab-trbw WRS. The potency assays are the same as described for the DS.

- Summary of Product Design: Teprotumumab-trbw is supplied as a sterile, single-dose, preservative-free lyophilized powder for IV infusion in a (b) (4) vial. Teprotumumab-trbw is formulated in (b) (4) histidine, (b) (4) trehalose, and (b) (4) polysorbate 20 at pH 5.5. Reconstitution with 10 (b) (4) mL sterile water for injection (WFI) yields a solution containing approximately 50 mg/mL teprotumumab-trbw. The deliverable amount is 500 mg.

- List of Excipients: Excipients include L-Histidine, L-Histidine hydrochloride monohydrate, α, α-trehalose dihydrate, and polysorbate 20. All excipients are compendial.

- Reference Materials: The same reference material is used for DS and DP.

- Manufacturing process summary: (b) (4)
(b) (4)

- Container closure: The primary container closure system for teprotumumab-trbw DP consists of a (b) (4) vial with a (b) (4)
(b) (4)
(b) (4) cap
(b) (4).

- Dating period and storage conditions: The dating period for teprotumumab-trbw DP is 18 months when stored at 2-8°C, protected from light. Storage conditions at room temperature for no more than 4 hours or at 2-8°C for no more than 48 hours are proposed for the reconstituted and diluted drug product in the sterile WFI.

- List of co-package components, if applicable: None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:
   a. Storage at 2-8°C.
   b. Store in original carton until time of use.
   c. Protect from light until use.
   d. Do not freeze.
   e. Do not shake.

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)			Approve – Based on PAI/PLI conducted on 10/28/2019-11/05/2019	FDA Form-483 issued (8-items), VAI	Approve
			Approve- Based on Previous History	N/A	Approve
			Approve- Based on Previous History	N/A	Approve
			Approve- Based on Previous History	N/A	Approve

(b) (4)					
			No Evaluation Necessary	N/A	Approve
			No Evaluation Necessary	N/A	Approve
			Approve- Based on Previous History	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)			Approve – Based on PAI/PLI conducted on 10/07-11 and 10/15-18, 2019	FDA Form-483 issued (5-item), VAI	Approve
			Approve- Based on Previous History	N/A	Approve

	(b) (4)				

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, process equipment cleaning, and contamination control strategy were provided (b) (4) (b) (4) and (b) (4) proposed for teprotumumab DP and DS manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved: Annual stability protocol for DS
ii. Outstanding review issues/residual risk: See PMCs 1, 2, 3, and 6
iii. Future inspection points to consider: Adequacy of investigations regarding manufacturing and laboratory deviations, evaluation of the trending programs implemented for monitoring the performance of the potency assay and the stability of the WRS against the internal potency assay quality control.

b. Drug Product

i. Protocols approved: Annual stability protocol for DP
ii. Outstanding review issues/residual risk: See PMCs 1, 2, 3, 4, 5, and 7
iii. Future inspection points to consider: None.

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/

KRISTEN P NICKENS
12/16/2019 05:19:27 PM

QING ZHOU
12/16/2019 06:06:06 PM

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **12/9/2019**
To: Administrative File, **STN 761143/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPMA/DBM/Branch I
Endorsement: Reyes Candau-Chacon, Ph.D., CDER/OPQ/OPMA/DBM/Branch II
Subject: New Biologic License Application (BLA)
Applicant: Horizon Pharma Ireland, Ltd.
US License: **2022**
Facility: (b) (4)
Product: teprotumumab-trbw (trade name pending)
Dosage: Lyophilized powder, 500 mg/vial, intravenous infusion
Indication: For the treatment of Active Thyroid Eye Disease
PDUFA date: March 6, 2020

Recommendation: The drug product part of this BLA, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective with the following post-marketing commitment:

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

Review Summary

Horizon has submitted this new Biologics License Application (BLA) for teprotumumab, a recombinant humanized monoclonal antibody for the treatment of active thyroid eye disease. The drug substance (DS) is manufactured at (b) (4). The drug product (DP) is manufactured at (b) (4) This application contains CMC information in an eCTD format.

This review contains an assessment of the teprotumumab drug product section of the BLA from a sterility assurance and product quality microbiology perspective. The amendments reviewed are provided in the table below:

Sequence number	Date	Description
0001	7/8/2019	Original BLA submission
0012	10/17/2019	Response to IR
0016	11/5/2019	Response to IR
0017	11/6/2019	Response to IR
0018	11/7/2019	Response to IR
0023	11/15/2019	Response to IR

0029	12/3/2019	Response to IR
0030	12/9/2019	Response to IR

Assessment

Drug Product

Description of the Composition of the Drug Product (3.2.P.1):

Teprotumumab drug product is a sterile, preservative-free, lyophilized powder for reconstitution and dilution for infusion. Each vial delivers 500 mg of teprotumumab formulated in (b) (4) histidine, (b) (4) trehalose and (b) (4) polysorbate 20, pH 5.5. The composition of the DP is provided in Table 1 in this section of the BLA.

Reviewer comment: The information on DP composition is adequately provided.

Satisfactory

Pharmaceutical Development (3.2.P.2):

Teprotumumab is a recombinant human monoclonal antibody and an insulin-like growth factor-1 receptor inhibitor.

Microbiological Attributes (3.2.P.2.5)

Container closure integrity (CCI) test

The drug product primary container closure is a (b) (4) vial which is closed with a (b) (4) (b) (4) top.

(b) (4)

3 Pages Have Been Withheld In Full As B4(CCI/TS) Immediately Following This Page

(b) (4)

Satisfactory

Manufacture (3.2.P.3):

(b) (4)

Bach formula (3.2.P.3.2)

The batch formula of the maximum validated batch size is (b) (4) (b) (4). The batch formula of the minimum validated batch size is (b) (4) (b) (4). The batch formula for the maximum and minimum batches are provided.

Satisfactory

Description of the Manufacturing Process and Process Controls (3.2.P.3.3) and Controls of Critical Steps and Intermediates (3.2.P.3.4)

(b) (4)

42 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Conclusion

I. The drug product section of the BLA, as amended, is recommended for approval from a sterility assurance and product quality microbiology perspective with the following post-marketing commitment:

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

II. Information and data in this submission not related to drug product sterility assurance and product quality microbiology perspective were not evaluated and should be reviewed by an OBP reviewer.

III. See panorama for GMP status of the relevant facilities.

Bo Chi

Digitally signed by Bo Chi
Date: 12/09/2019 04:10:00PM
GUID: 508da71600029713f321cfd33c82d8d4

Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 12/09/2019 04:27:33PM
GUID: 508da7160002977f7ca389c8f849b707