

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761232Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary

Assessment Date: 1/12/2024

1. Application/Product Information

BLA number	761232
Submission Type	Original Submission
Regulatory Pathway	351(a), new molecular entity
Associated IND/BLA	IND 126875
Review Designation	Standard
Applicant	BeiGene USA, Inc.
Indication	Treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Tevimbra
	Non-proprietary Name: Tislelizumab-jsgr
	Code Name: BGB-A317
	OBP Naming: MAB HUMANIZED (IGG4) ANTI Q15116 (PDCD1_HUMAN)[BGB-A317]
Drug Product Description	BGB-A317 drug product is a clear to slightly opalescent, colorless to slightly yellow solution. It is supplied in a vial as a sterile, single-use, preservative-free solution intended for intravenous infusion, containing 100 mg drug product. The vial contains 10.0 mL extractable volume of 10 mg/mL tislelizumab-jsgr (drug substance), (b) (4) citrate, (b) (4) histidine, (b) (4) trehalose-polysorbate 20 at pH 6.5.

	BGB-A317 drug substance is a recombinant humanized monoclonal antibody (IgG4) that specifically binds to human PD-1.		
Dosage Form	Injection (solution)		
Strength	10 mg/mL		
Route of Administration	Intravenous infusion		
Primary Container Closure System	Vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Anshu Rastogi	Brian Janelins
	Drug product	Eun Hee Koh	
	Immunogenicity Assay	Eun Hee Koh	
	Facility	Wendy Tan (DS), Lindsey Brown (DP)	Zhong Li
	Microbiology		Maxwell Van Tassell
	RBPM	Andrew Shiber	
	ATL	Brian Janelins	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761232 for Tevimbra manufactured by BeiGene USA, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Tevimbra is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** Boehringer Ingelheim Biopharmaceuticals (China) Ltd. (FEI 3015009021)
- **Drug Product:** Boehringer Ingelheim Biopharmaceuticals (China) Ltd. (FEI 3015009021)

b. Fill size and dosage form: 100 mg/10 mL solution, injection

c. Dating Period:

- **Drug Product:** 36 months at 5°C
- **Drug Substance:** (b) (4) months at (b) (4) °C
- **Stability Option:**
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance under 21 CFR 601.12.

d. Exempt from lot release:

- Yes, Tevimbra is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable

PMCs (OPMA)

1. Develop a reliable endotoxin detection method that can overcome the LER phenomenon for the tislelizumab drug product.
2. Implementation of in-line pressure monitoring of sterile filtration for the tislelizumab drug product

4. Basis for Recommendation

a. Summary:

BGB-A317 is a recombinant humanized monoclonal antibody (IgG4) that specifically binds to human PD-1. Binding of BGB-A317 to PD-1 inhibits PD-1-mediated negative signaling and enhances the functional activity of T cells.

BGB-A317 was engineered to minimize binding to Fcγ receptors on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T cell clearance and potential resistance to anti-PD-1 therapy.

Two assays, which include a binding assay and a cell-based assay, are used to control the potency of BGB-A317 drug substance and drug product. The binding assay is an ELISA that measures the binding activity of BGB-A317 to human PD-1. The cell-based assay is a functional assay that measures the ability of BGB-A317 to block cell surface PD-1 from engaging with the target ligand PD-L1, resulting in abrogation of downstream receptor signaling events. The assay uses a human T cell line, HuT78/P3Z, which was engineered to express a chimeric PD-1 receptor (P3Z) in which the cytoplasmic domain of human PD-1 was replaced with the cytoplasmic domain of human CD3ζ chain. In addition, the assay uses HEK293 cells, which were engineered to stably express surface human PD-L1. When the chimeric PD-1/CD3ζ receptor on the HuT78/P3Z cells is engaged by the PD-L1 on the HEK293 cells, IL-2 is expressed. When both cell lines are incubated with BGB-A317, there is a dose-response abrogation of IL-2 expression. Measurement of the inhibition of IL-2 secretion by ELISA is used to inform potency activity. All potency results for the binding and cell-based assays are reported as a percentage relative to a qualified reference standard.

The drug substance manufacturing process consists of

(b) (4)

The overall BGB-A317 control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Tevimbra (BGB-A317) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern.

The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for the Boehringer Ingelheim Biopharmaceuticals (China), Ltd. facility (FEI 3015009021), which is proposed for BGB-A317 drug substance and drug product manufacture. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from product quality, facility, microbiology, and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate with PMCs/PMRs

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for Tevimbra (i.e., there is no specific test method described in regulation for Tevimbra that establishes an official standard of potency). We next considered whether potency is a factor for Tevimbra within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Tevimbra for purposes of § 610.61(r) because lot variability is not a concern for Tevimbra as Tevimbra's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

- i. Protocols approved:

1. (b) (4) monitoring protocol
2. (b) (4)
3. (b) (4)
4. (b) (4)
5. (b) (4)
6. Drug substance annual stability protocol (with shelf-life extension)
 - ii. Residual risk: None
 - iii. Future inspection points to consider: None

c. Drug Product:

- i. Protocols approved:
 1. Drug product annual stability protocol (no shelf-life extension)
- ii. Residual risk: None
- iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.



Rachel
Novak

Digitally signed by Rachel Novak

Date: 1/12/2024 03:17:54PM

GUID: 52e163f70002ba9e745b4e39384c76d7



Brian
Jannelsins

Digitally signed by Brian Jannelsins

Date: 1/12/2024 02:01:22PM

GUID: 54b8280e000855ed28b059d11c54a788



U.S. FOOD & DRUG
ADMINISTRATION

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	January 11, 2024
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Eun Hee Koh, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761232
Applicant:	BeiGene USA, Inc
Submission Date:	July 10, 2021
Product:	Tevimbra (tislelizumab-jsgr)
Dosage form(s):	Injection
Strength and Container-Closure:	100 mg/10 mL (10 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of tislelizumab-jsgr for the treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are acceptable 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)

CONCLUSION

The prescribing information, medication guide, container labels, and carton labeling submitted on January 10, 2024 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on July 12, 2021)
<\\CDSESUB1\evsprod\bla761232\0001\m1\us\draft-labeling-text.doc>
- Medication Guide (submitted on July 12, 2021)
<\\CDSESUB1\evsprod\bla761232\0001\m1\us\medication-guide.pdf>
- Container Labels (submitted on July 12, 2021)

(b) (4)

Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ 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
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ 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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S. license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.</i>	

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

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.

⁵ Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

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

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ 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
<i>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</i>	☒ 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 limited space considerations. See carton.	

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

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. <i>The applicant confirms there is no text on the ferrule and cap overseal of the vials.</i>	

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. <i>The applicant confirms that the vial provides a 4 x 35 mm uncovered area to allow for visual inspection when the label is affixed to the vial. The 20 mL vial has a circumference of 94.2 mm and the label dimensions are 90 x 28 mm.</i>	

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

<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider revising the route of administration statement from (b) (4) to read "For Intravenous Infusion After Dilution" to be consistent with the carton labeling. <i>The applicant revised as requested.</i>	

<u>NDC numbers (container label)</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

<u>Preparation instructions (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: 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</i>	☐ Yes ☐ No ☒ N/A

<u>Package type term (container label)</u>	<u>Acceptable</u>
<i>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</i>	☒ Yes ☐ No ☐ N/A

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

<u>Prominence of required label statements (container label)</u>	<u>Acceptable</u>
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
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>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</i>	☒ Yes ☐ No ☐ N/A

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
<i>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</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ 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
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

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

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

Package⁶ 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
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

⁶ 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.

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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ 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

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

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ 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

<i>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</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
---	--

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

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
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ 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
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the inactive ingredients names to its compendial name and adjust the quantity to fulfill FDCA section 502(e) as follows: "Each 10 mL vial contains 100 mg of tislelizumab-xxxx, citric acid monohydrate (4.2 mg), histidine (17.2 mg), L-histidine hydrochloride monohydrate (8.2 mg), polysorbate 20 (2.0 mg), sodium citrate (59.3), trehalose (650.4 mg), and (b) (4) Water for Injection, USP." <i>The applicant revised as requested.</i> Revise the inactive ingredient list so the diluent appears at the end: "Each 10 mL vial contains 100 mg of tislelizumab-jsgr, citric acid monohydrate (4.2 mg), histidine (17.2 mg), L-histidine hydrochloride monohydrate (8.2 mg), polysorbate 20 (2 mg), sodium citrate (59.3 mg), trehalose (650.4 mg) in (b) (4) Water for Injection, USP. No preservative." <i>The applicant revised as requested.</i>	

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
Comment/Recommendation: <i>Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for tislelizumab products (i.e., there is no specific test method described in regulation for tislelizumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Tevimbra because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.</i> Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable. <i>The applicant revised as requested.</i>	

<u>Rx only (package labeling)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

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

<u>Distributor (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

<u>Bar code (package labeling)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

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

<u>NDC numbers (package labeling)</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
<i>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</i> <i>USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	Acceptable
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider relocating the statement "Discard unused portion." to appear after the package type term "One Single-dose Vial". <i>The applicant revised as requested.</i>	

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
<i>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</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

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 dosage statement from (b) (4) See Prescribing Information." to "Dosage: See Prescribing Information." to avoid clutter. <i>The applicant revised as requested.</i>	

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We added a placeholder for the 4-letter suffix to the proper name. <i>The applicant revised as requested.</i>	

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

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv)] <i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter</i>	☒ Yes ☐ No ☐ N/A

<i>and discoloration prior to administration, whenever solution and container permit."</i>	
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." per 21 CFR 201.57(c)(3)(iv). <i>The applicant revised as requested.</i>	

Full Prescribing Information	
<u>3 DOSAGE FORMS AND STRENGTHS</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Added strength per mL enclosed in parenthesis to appear after the strength per total volume. <i>The applicant revised as requested.</i>	

Full Prescribing Information	
<u>11 DESCRIPTION</u>	<u>Acceptable</u>
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
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised inactive ingredients in alphabetical order. <i>The applicant revised as requested.</i>	

We revised inactive ingredients to their compendial names (b) (4)

if needed to fulfill FDCA section 502(e).

The applicant revised as requested.

Added pH information per 21 CFR 201.57(c)(12)(ii).

The applicant revised as requested.

We revised the inactive ingredient list, so the diluent appears at the end.

The applicant revised as requested.

Full Prescribing Information	
15 & 16 Hazardous Drug	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv)	☐ Yes ☐ No ☒ N/A
Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html	
Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures. ¹	

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Added strength per mL enclosed in parenthesis to appear after the strength per total volume. <i>The applicant revised as requested.</i>	

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

(Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	
--	--

Medication Guide Evaluation

MEDICATION GUIDE	
<u>TITLE (NAMES AND DOSAGE FORM)</u>	<u>Acceptable</u>
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We added a placeholder for the 4-letter suffix to the proper name. <i>The applicant revised as requested.</i>	

MEDICATION GUIDE	
<u>STORAGE AND HANDLING</u>	<u>Acceptable</u>
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

MEDICATION GUIDE	
<u>INGREDIENTS</u>	<u>Acceptable</u>
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised inactive ingredients in alphabetical order and revised inactive ingredient names to be consistent with the Prescribing Information. <i>The applicant revised as requested.</i>	

MEDICATION GUIDE	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 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

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on January 10, 2024)

18

19 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page



Jennifer
Kim

Digitally signed by Jennifer Kim

Date: 1/11/2024 09:10:35PM

GUID: 5e5438d2008138bdbae1db8d4abc0580



Eun
Koh

Digitally signed by Eun Koh

Date: 1/12/2024 08:46:04AM

GUID: 5e3b089f00b207a10410177924a29b94