# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761416Orig1s000

# PRODUCT QUALITY REVIEW(S)

# OPQ Executive Summary Addendum
# Date: 11/20/2024

This OPQ BLA executive summary addendum provides a correction for zanidatamab-hrii drug substance shelf life from (b) (4) months at (b) (4) °C to (b) (4) months at (b) (4) °C.

## 1. Application/Product Information

| | |
|---|---|
| BLA number | 761416 |
| Submission Type | Original Submission<br>(Fast Track, Orphan Drug, Breakthrough Therapy Designation) |
| Regulatory Pathway | NME 351(a) |
| Associated IND | IND (b) (4) |
| Review Designation | Priority Review |
| Applicant | Jazz Pharmaceuticals Ireland Limited |
| Indication | Treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced (unresectable) or metastatic biliary tract cancer (BTC). |
| Rx/OTC dispensed | Rx |
| Drug Product Name | Proprietary Name: ZIIHERA |
| | Non-proprietary Name/Code Name:<br>Zanidatamab-hrii |
| | OBP Naming: MAB HUMANIZED (IGG1) T350V, L351Y, F405A, Y407V (CHAIN A) & C220S, T350V, T366L, K392L, T394W (CHAIN B) ANTI P04626 (ERBB2_HUMAN) [ZW25] |
| Drug Product Description | ZIIHERA (zanidatamab-hrii) for injection is a sterile, preservative-free, white, lyophilized powder supplied in 300 mg strength in a single-dose (b) (4) vial for |

| | | | |
|---|---|---|---|
| | reconstitution and further dilution stored at 2ºC to 8ºC (36ºF to 46ºF). Each vial contains zanidatamab-hrii (300 mg), (b) (4) succinate (4.3 mg), succinic acid (4.3 mg), sucrose (567 mg), and polysorbate 20 (0.63 mg), pH 4.6. After reconstitution with 5.7 mL of Sterile Water for Injection the resulting concentration is 50 mg/mL ZIIHERA.<br><br>Zanidatamab is a humanized, bispecific, IgG1-like antibody consisting of a Fab arm and a scFv arm directed against two non-overlapping epitopes of the extracellular domain of the human HER2 antigen. These epitopes are the same epitopes that are recognized by trastuzumab (scFv arm) and pertuzumab (Fab arm). Binding of zanidatamab with HER2 induces formation of receptor clusters and receptor internalization resulting in reduced HER2 expression. Zanidatamab inhibits ligand-dependent and independent tumor cell growth and potently activates antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). | | |
| **Dosage Form** | Lyophilized powder for injection | | |
| **Strength** | 300 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution | | |
| **Route of Administration** | Intravenous (IV) Infusion | | |
| **Primary Container Closure System** | (b) (4) Type (b) (4) clear colorless glass vial, closed with an (b) (4) rubber stopper and an aluminum seal flip-off cap with a (b) (4) plastic cap overseal. | | |
| **Device Information** | Not applicable | | |
| **Co-packaged Product Information** | Not applicable | | |
| | **Discipline** | **Primary** | **Secondary** |
| | Drug substance | Emine GuvenMaiorov | Jun Liu |
| | Drug product | | |

| | | | |
|---|---|---|---|
| **OPQ Review Team** | Immunogenicity Assay | Rachel Lokanga | Ian McWilliams |
| | Facility | Hamet Toure | Madushini Dharmasena |
| | Microbiology | | |
| | CMC Labeling | Liming Lu | |
| | RBPM | Kelly Ballard | |
| | ATL | Jun Liu | |
| | OPQA Review Chief | Maria-Teresa Gutierrez-Lugo | |
| **OPQ Issued Consults** | Not applicable | | |

## 2. Recommendation and Conclusion on Approvability

**Recommendation: Approval with PMCs/PMRs**

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761416 for ZIIHERA (zanidatamab-hrii) manufactured by (b) (4) The data submitted in this application are adequate to support the conclusion that the manufacture of ZIIHERA (zanidatamab-hrii) 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:** (b) (4)
- **Drug Product:**
  - Manufacturing: (same as drug substance)
  - Labeling and secondary packaging: (b) (4)

### b. Fill size and dosage form:

300 mg of lyophilized powder in a single-dose vial

### c. Dating Period:

- **Drug Substance:**

(b) (4) months at (b) (4) °C

- Intermediate Substance, if applicable: Not applicable
- For packaged products:
  - Drug Product: 24 months at 2-8°C
- 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.

d. Exempt from lot release:
   - Yes
   - ZIIHERA 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

**Three PMCs from OPQA III are listed below:**

1) To implement a two-tiered reference standard (RS) system consisting of primary and working RS (PRS and WRS), prior to the depletion of the current RS, through the submission of a prior approval supplement (PAS) per 21 CFR 601.12. Protocols including qualification of future PRS and WRS and requalification of PRS and WRS, should be included in the PAS.

   Final protocol submission date: 01/2025

2) To update the drug substance and drug product release and stability specifications for zanidatamab to include a validated C1q binding ELISA method with justified quantitative acceptance criteria, as a surrogate method to control the complement dependent cytotoxicity (CDC) activity. The updated specifications, method validation data, and other supporting information will be submitted to the BLA as a PAS per 21 CFR 601.12.

   Final report submission date: 06/2026

3) To develop, validate, and implement a test method for control of (b) (4) with justified quantitative acceptance criteria in the drug substance release specification for zanidatamab. The updated specification, method validation report, and any other supporting information will be submitted to the BLA as a PAS per 21 CFR 601.12.

Final Report Submission: 03/2026

## 4. Basis for Recommendation

### a. Summary:

Zanidatamab-hrii (also known as JZP598 and ZW25) is a humanized, bispecific, IgG1-like monoclonal antibody directed against the juxtamembrane extracellular domain (ECD4) and the dimerization domain (ECD2) of human epidermal growth factor receptor 2 (HER2). The ECD4 and ECD2 are the same domains that can be recognized by trastuzumab and pertuzumab, respectively. Binding of zanidatamab with HER2 induces formation of receptor clusters and receptor internalization resulting in reduced HER2 expression, leads to inhibition of growth factor-dependent and independent tumor cell proliferation, and potentially activates Fc-dependent effector functions, ADCC, CDC and ADCP. It is indicated for treatment of patients with HER2-positive, locally advanced (unresectable) or metastatic biliary tract cancer (BTC).

Four assays are used to control the potency of ZIIHERA (zanidatamab-hrii).

(b) (4)

The drug substance manufacturing process consists of

(b) (4)

(b) (4)

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations. An on-site pre-licensing inspections (PLI) for the drug substance and drug product manufacturing facilities at (b) (4) and found satisfactory.

Results of the immunogenicity assays, the ADA and Nab assays, demonstrated that they were able to identify ADA and NAb positive individuals in post-treated samples, supporting the assay is fit-for-purpose. However, the risk of false-positive increases as the levels of soluble HER2 (sHER2) increase, which can over-estimate ADA positivity. OPQ recommends that the "treatment-emergent" definition is not used due to interference in pre-dose samples and that all post-treatment ADA samples above cut-point be considered positive to capture ADA positive status. After discussion with the clinical pharmacology review team, it was determined that they would like to request a PMC because of the impact to data interpretability with ADA false-positive.

The overall ZIIHERA (zanidatamab-hrii) 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 ZIIHERA (zanidatamab-hrii) 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 BLA is recommended for approval from the product quality, facility, microbiology and sterility assurance perspectives.

**b. Subdiscipline Recommendation:**

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

Microbiology - Adequate

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 ZIIHERA (i.e., there is no specific test method described in regulation for ZIIHERA that establishes an official standard of potency). We next considered whether potency is a factor for ZIIHERA 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 ZIIHERA for purposes of § 610.61(r) because lot variability is not a concern for ZIIHERA as ZIIHERA'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:
(b) (4)

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:
i. Protocols approved:
(b) (4)

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.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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JUN LIU
11/20/2024 01:16:38 PM

MARIA T GUTIERREZ LUGO
11/20/2024 01:31:31 PM

# LABELS AND LABELING ASSESSMENT

| | |
|---|---|
| Date of Assessment: | November 4, 2024 |
| Assessor: | Liming Lu, PharmD<br>Labeling Assessor<br>Office of Product Quality Assessment III (OPQA III) |
| Through: | Emine Guven-Maiorov, PhD<br>Product Quality Assessor<br>OPQA III/Division of Product Quality Assessment XV |
| Application: | BLA 761416 |
| Applicant: | Jazz Pharmaceuticals Ireland Limited |
| Submission Date: | March 29, 2024 |
| Product: | Ziihera (zanidatamab-hrii) |
| Dosage form(s): | For injection |
| Strength and Container-Closure: | 300 mg lyophilized powder in a single-dose vial |
| Purpose of assessment: | The Applicant submitted a biologics license application for the approval of Ziihera (zanidatamab-hrii) for treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced (unresectable) or metastatic biliary tract cancer. |
| **Recommendations:** | The prescribing information, patient information, container labels, and carton labeling are **acceptable** from an OPQA III 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 and patient information (submitted on November 1, 2024), container labels (submitted on October 18, 2024), and carton labeling (submitted on October 22, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

## APPENDICES

**Appendix A**: Proposed Labeling

- Prescribing Information and Patient Information (submitted on March 29, 2024) \\CDSESUB1\EVSPROD\bla761416\0006\m1\us\uspi.docx
- Container Labels (submitted on March 29, 2024) \\CDSESUB1\EVSPROD\bla761416\0006\m1\us\draft-vial-label.pdf

(b) (4)

**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), 21 CFR 600.3(k) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)* | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (using the qualifying phrase "Manufactured by:")* | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (U.S license number for container bearing a partial label[5])* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** The name, address, and license number of the manufacturer shall appear on the container label per 21 CFR 610.60 (a)(2). FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not

[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."

limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, the applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. Confirm "Jazz Pharmaceuticals Ireland Limited" is the manufacturer. Revise the licensed manufacturer to appear as:

Manufactured by: Jazz Pharmaceuticals Ireland Limited
Address as listed on line 5 of Form FDA 356h
US License No. 2167

*The applicant has revised as requested.*

| **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<br>☐ No<br>☐ N/A |

| **Expiration date (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: USP General Chapters <7> Labeling,* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☒ N/A |

| **Product Strength (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (expression of strength for injectable drugs) references:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** As currently presented, the strength statement is presented as [redacted] (b) (4) [redacted]. Revise the strength statement to read "300 mg/ vial" in accordance with *USP General Chapter <7>*. For example:

Ziihera
(zanidatamab-hrii)
For injection
300 mg/vial

| |
|---|
| *The applicant has revised as requested.* |

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

| **Statement: "Rx only" (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (prominence of Rx Only statement) reference:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) | ✓ Yes<br>☐ No<br>☐ N/A |

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

| |
|---|
| **Comment/Recommendation:** The product does not need a Medication Guide. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7). |

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

| |
|---|
| **Comment/Recommendation:** The container is enclosed in a package. |

| **No container label (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.60(d) | ☐ Yes<br>☐ No<br>☒ N/A |

| |
|---|
| **Comment/Recommendation:** The product contains a container label. |

| **Ferrule and cap overseal** *(for vials only)* | **Acceptable** |
|---|---|
| *Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Confirm there is no text on the ferrule and cap overseal of the vials.

*The applicant responded that* (b) (4) (b) (4)

| **Visual inspection** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.60(e) | ✓ Yes<br>☐ No<br>☐ 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.

*The circumference of the vial is 94 mm, and the width of the vial label is 84 mm, allowing 10 mm of the vial uncovered to allow for visual inspection. See below for the visual rendering of the affixed label on the vial:*

(b) (4)

| **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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)* | ✓ Yes<br>☐ No<br>☐ N/A |

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

| **Preparation instructions (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.5(g) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) | ✓ Yes<br>☐ No<br>☐ N/A |

| **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)<br>*USP chapter <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** For injectable drugs for parenteral administration, the inclusion of the package type term on container labels and carton labeling is important. Recommend adding the package type term "single-dose vial" to the container label.

*The applicant has added the package type term statement "single-dose vial. Discard unused portion." to the container label, which is acceptable.*

| **No misleading statements (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.6 | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Remove the statement "No U.S. standard of potency" from the container label because our view is that 21 CFR 610.61(r) is not applicable.

*The applicant has revised as requested.*

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

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

| **Comment/Recommendation:** The label does not display text in Spanish. |
|---|

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

| **Comment/Recommendation:** The drug product does not contain FD&C Yellow No. 5 or 6. |
|---|

| **Bar code label requirements (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 201.25, 21 CFR 610.67 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references:* Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011)<br>Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) | ✓ Yes<br>☐ No<br>☐ N/A |

| **Comment/Recommendation:** Ensure the linear bar code is surrounded by enough white space to facilitate proper scanning.<br><br>*The applicant has confirmed that the linear bar code appears and follows GS1 standards.* |
|---|

| **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<br>☐ No<br>☒ N/A |

| **Net quantity (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.51 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)<br>Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015)<br>*USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).* | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |

| **Inactive ingredients (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.100, FD&C Act section 502(e) | ☐ Yes<br>☐ No<br>☒ N/A |
| *Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling* | ☐ Yes<br>☐ No<br>☒ N/A |

**Comment/Recommendation:** The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required. See package labeling comment.

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

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

## Package[6] Labeling Evaluation

| **Proper name (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2), 21 CFR 600.3(k) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Propriety name, proper name, dosage form, product strength, and route(s) of administration are the critical information which should be the most prominently displayed information on the principal display panel (PDP) of the carton. See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022). The strength is currently presented (b) (4) Recommend relocating the strength statement "300 mg/vial" so that it is immediately located below the proprietary name, nonproprietary name,

[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.

and dosage form "for injection" on the PDP of the carton to facilitate proper identification of the product.

*The applicant has revised as requested.*

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

**Comment/Recommendation:** For biologic products, the name of Applicant in Field 2 of the form FDA 356h is the name of the person or legal entity to whom the license will be issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. Confirm "Jazz Pharmaceuticals Ireland Limited" is the manufacturer. Revise the licensed manufacturer to appear as:

Manufactured by: Jazz Pharmaceuticals Ireland Limited
Address as listed on line 5 of Form FDA 356h
US License No. 2167

Clarify the role of [redacted] (b) (4) The applicant may include the drug product facility to the carton labeling when there is adequate space and the licensed manufacturer is on the carton labeling. If this is the drug product facility, it should appear as: "Manufactured at: Drug Product Facility Name and address".

*The applicant has revised the manufacturer information on the carton labeling (Seq#0027). However, the following recommendation has been sent to the applicant for implementation:* The applicant may include the Country of Origin per U.S. Customs Border and Protection regulations 19 CFR 134.11. The labeling should appear as: Product of Country of Origin. Revise the Country of Origin statement to read as: [redacted] (b) (4)

*The applicant has revised as requested.*

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

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

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

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

| **Number of containers (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(f) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

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

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

| **Multiple dose containers (recommended individual dose) (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(j) | ☐ Yes<br>☐ No<br>☒ 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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)* | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☒ N/A |

**Comment/Recommendation:** The product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

| **Inactive ingredients (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e), the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, sodium succinate, polysorbate 20, succinic acid, and sucrose. We also revised the inactive ingredients list in alphabetic order as recommended in *USP General Chapters <7> Labeling*. The inactive ingredients list on the side panel of the carton should read as:
"Each single-dose vial of reconstituted product contains 300 mg of zanidatamab-hrii and the inactive ingredients: polysorbate 20 (0.63 mg), sodium succinate (4.3 mg), succinic acid (4.3 mg), and sucrose (567 mg)."

*The applicant has revised the inactive ingredients list as requested but using* (b) (4) *s recommended in FDA draft guidance "Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs (April 2024).*
We did not agree. Applicants must list the established name of inactive ingredients in the statement of ingredients in a drug product's labeling, per Section 502(e)(1)(A)(iii) of the FD&C Act. Sodium succinate is the current official USP monograph title. Therefore, revise the inactive ingredients list to read as:
"Each single-dose vial contains 300 mg of zanidatamab-hrii and the inactive ingredients: polysorbate 20 (0.63 mg), sodium succinate (4.3 mg), succinic acid (4.3 mg), and sucrose (567 mg)."

*The applicant has revised as requested.*

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

| **Minimum potency of product (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(r) | ☐ Yes<br>☐ No<br>☒ N/A |

**Comment/Recommendation:** Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for **zanidatamab** products (i.e., there is no specific test method described in regulation for **zanidatamab** 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 **Ziihera** 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.

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.

*The applicant has revised as requested.*

| **Rx only (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) | ✓ Yes<br>☐ No<br>☐ N/A |

| **Divided manufacturing (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics) | ☐ Yes<br>☐ No<br>☒ N/A |

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

| **Bar code (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.67, 21 CFR 201.25 | ✓ Yes<br>☐ No<br>☐ N/A |
| Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011)<br>Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☒ N/A |

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

| **Preparation instructions (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)<br>*USP General Chapters <7> Labeling* | ✓ Yes<br>☐ No<br>☐ 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)<br>*USP chapter <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |

| **No misleading statements (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.6 | ✓ Yes<br>☐ No<br>☐ N/A |

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

| **Comment/Recommendation:** See previous package labeling comment for dosage form and product strength under Proper name. |
|---|

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

| **Comment/Recommendation:** The label does not display text in Spanish. |
|---|

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

| **Comment/Recommendation:** The drug product does not contain FD&C Yellow No. 5 or 6. |
|---|

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

| **Comment/Recommendation:** The drug product does not contain phenylalanine. |
|---|

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

| **Comment/Recommendation:** The drug product does not contain sulfites. |
|---|

| **Net quantity (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.51 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)<br>Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015)<br>*USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).* | ✓ Yes<br>☐ No<br>☐ N/A |

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

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

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

## Prescribing Information Evaluation

**PRESCRIBING INFORMATION**

| **Highlights of Prescribing Information** | |
|---|---|
| **PRODUCT TITLE** | **Acceptable** |
| Regulation: 21 CFR 201.57(a)(2) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |

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

| | |
|---|---|
| *USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling* | |

| **Full Prescribing Information** | |
|---|---|
| **2 DOSAGE AND ADMINISTRATION** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(3)(iv)<br>*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 and discoloration prior to administration, whenever solution and container permit."* | ✓ Yes<br>☐ No<br>☐ N/A |
| *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*<br>Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023) | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:**
Revised to the required verbatim statement for parenterals per 21 CFR 201.57(c)(3)(iv).

Revised to "…with no visible particles." for clarity.

Revised to the compendial names for the diluents.

Revised to "…up to 4 hours…" for the maximum in-use duration of the reconstituted solution based on the evaluation of the submitted micro-stability data.

*The applicant has revised as requested.*

| **Full Prescribing Information** | |
|---|---|
| **3 DOSAGE FORMS AND STRENGTHS** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(4) | ✓ Yes<br>☐ No<br>☐ 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)<br>*USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** We removed information that is not required in section 3.

**3 DOSAGE FORMS AND STRENGTHS**

For injection: 300 mg (b) (4) white lyophilized powder in a single-dose vial (b) (4) (b) (4)

*The applicant has revised as requested.*

| **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), FD&C Act Section 502(e) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** We revised to include the dosage form in the second paragraph of section 11 per 21 CFR 201.57(c)(12)(i)(B).

Revised to include the deliverable volume information when the product is to be reconstituted.

*The applicant has revised as requested.*

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e), the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, polysorbate 20, sodium succinate, succinic acid, and sucrose. We also revised the inactive ingredients list in alphabetic order as recommended in *USP General Chapters <1091> Labeling of Inactive Ingredients*.

*The applicant has revised the inactive ingredients list as requested but using* (b) (4) *s recommended in FDA draft guidance "Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs (April 2024).*

*Comment to Applicant: We did not agree with the revision. Applicants must list the established name of inactive ingredients in the statement of ingredients in a drug product's labeling, per Section 502(e)(1)(A)(iii) of the FD&C Act. We revised to the established name "sodium succinate" in the label/labeling because "sodium succinate" is the current official USP monograph title.* (b) (4)

*The applicant has revised as requested for "sodium succinate" in the label.*

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

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

| Full Prescribing Information | |
|---|---|
| **MANUFACTURER INFORMATION** | **Acceptable** |
| Regulations: 21 CFR 201.100(e), 21 CFR 201.1 | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** For biologic products, the name of Applicant in Field 2 of the form FDA 356h is the name of the person or legal entity to whom the license will be issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. **Confirm** "Jazz Pharmaceuticals Ireland Limited" is the manufacturer. Revise the licensed manufacturer to appear as:
Manufactured by:
Jazz Pharmaceuticals Ireland Limited
Address as listed on line 5 of Form FDA 356h
US License No. 2167

Clarify the role of [redacted] (b) (4) If this is the drug product facility, which is not required but can be listed as: "Manufactured at: Drug Product Facility Name and address".

*The applicant has confirmed that "Jazz Pharmaceuticals Ireland Limited" is the manufacturer and revised manufacturer information as requested. (b) (4) was deleted from the label as it is the drug substance and drug product manufacturing facility, which is acceptable from OPQA III labeling perspective.*

## Patient Information Labeling Evaluation

| PATIENT INFORMATION LABELING | |
|---|---|
| **TITLE (NAMES AND DOSAGE FORM)** | **Acceptable** |
| *Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).* | ✓ Yes<br>☐ No<br>☐ N/A |

| PATIENT INFORMATION LABELING | |
|---|---|
| **STORAGE AND HANDLING** | **Acceptable** |
| *Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)* | ☐ Yes<br>☐ No<br>☒ N/A |

| PATIENT INFORMATION LABELING | |
|---|---|
| **INGREDIENTS** | **Acceptable** |
| *Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients), the established names for inactive ingredients in your products are revised according to the USP/NF monographs titles. Also, inactive ingredients names have been revised to appear in alphabetical order according to *USP General Chapters <1091> Labeling of Inactive Ingredients*.

*The applicant has revised as requested.*

| PATIENT INFORMATION LABELING | |
|---|---|
| **MANUFACTURER INFORMATION** | **Acceptable** |
| 21 CFR 201.1, 19 CFR 134.11 | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** For biologic products, the name of Applicant in Field 2 of the form FDA 356h is the name of the person or legal entity to whom the license will be issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. Confirm "Jazz Pharmaceuticals Ireland Limited" is the manufacturer. Revise the licensed manufacturer to appear as:
Manufactured by:
Jazz Pharmaceuticals Ireland Limited
Address as listed on line 5 of Form FDA 356h
US License No. 2167

Clarify the role of [redacted] (b) (4) If this is the drug product facility, which is not required but can be listed as: "Manufactured at: Drug Product Facility Name and address".

*The applicant has confirmed that "Jazz Pharmaceuticals Ireland Limited" is the manufacturer and revised manufacturer information as requested.* [redacted] (b) (4) *was deleted from the label as it is the drug substance and drug product manufacturing facility, which is acceptable from OPQA III labeling perspective.*

## APPENDIX C. Acceptable Labels and Labeling

*To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.*

- Prescribing Information and Patient Information (submitted on November 1, 2024) \\CDSESUB1\EVSPROD\bla761416\0041\m1\us\114-labeling\draft\labeling\draft-labeling-text-ms-word.docx
- Container Labels (submitted on October 18, 2024) \\CDSESUB1\EVSPROD\bla761416\0035\m1\us\114-labeling\draft\carton-and-container\draft-container-label.pdf


- Carton Labeling (submitted on October 22, 2024) \\CDSESUB1\EVSPROD\bla761416\0037\m1\us\114-labeling\draft\carton-and-container\draft-carton.pdf

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Liming Lu

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Emine GuvenMaiorov

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Date: 11/04/2024 11:36:40AM
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# BLA Executive Summary
# Assessment Date: 10/10/2024

## 1. Application/Product Information

| | |
|---|---|
| BLA number | 761416 |
| Submission Type | Original Submission<br>(Fast Track, Orphan Drug, Breakthrough Therapy Designation) |
| Regulatory Pathway | NME 351(a) |
| Associated IND | IND (b) (4) |
| Review Designation | Priority Review |
| Applicant | Jazz Pharmaceuticals Ireland Limited |
| Indication | Treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced (unresectable) or metastatic biliary tract cancer (BTC). |
| Rx/OTC dispensed | Rx |
| Drug Product Name | Proprietary Name: ZIIHERA |
| | Non-proprietary Name/Code Name:<br>Zanidatamab-hrii |
| | OBP Naming: MAB HUMANIZED (IGG1) T350V, L351Y, F405A, Y407V (CHAIN A) & C220S, T350V, T366L, K392L, T394W (CHAIN B) ANTI P04626 (ERBB2_HUMAN) [ZW25] |
| Drug Product Description | ZIIHERA (zanidatamab-hrii) for injection is a sterile, preservative-free, white, lyophilized powder supplied in 300 mg strength in a single-dose (b) (4) vial for reconstitution and further dilution stored at 2ºC to 8ºC (36ºF to 46ºF). Each vial contains zanidatamab-hrii (300 mg), (b) (4) succinate (4.3 mg), succinic acid (4.3 mg), sucrose (567 mg), and polysorbate 20 (0.63 mg), pH 4.6. After reconstitution with 5.7 mL of Sterile Water |

| | | | |
|---|---|---|---|
| | for Injection the resulting concentration is 50 mg/mL ZIIHERA.<br>Zanidatamab is a humanized, bispecific, IgG1-like antibody consisting of a Fab arm and a scFv arm directed against two non-overlapping epitopes of the extracellular domain of the human HER2 antigen. These epitopes are the same epitopes that are recognized by trastuzumab (scFv arm) and pertuzumab (Fab arm). Binding of zanidatamab with HER2 induces formation of receptor clusters and receptor internalization resulting in reduced HER2 expression. Zanidatamab inhibits ligand-dependent and independent tumor cell growth and potently activates antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). | | |
| **Dosage Form** | Lyophilized powder for injection | | |
| **Strength** | 300 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution | | |
| **Route of Administration** | Intravenous (IV) Infusion | | |
| **Primary Container Closure System** | (b) (4) Type (b) (4) clear colorless glass vial, closed with an (b) (4) rubber stopper and an aluminum seal flip-off cap with a (b) (4) plastic cap overseal. | | |
| **Device Information** | Not applicable | | |
| **Co-packaged Product Information** | Not applicable | | |
| | **Discipline** | **Primary** | **Secondary** |
| | Drug substance | Emine GuvenMaiorov | Jun Liu |
| | Drug product | | |
| | Immunogenicity Assay | Rachel Lokanga | Ian McWilliams |
| | Facility | Hamet Toure | Madushini |

| | | | |
|---|---|---|---|
| **OPQ Review Team** | Microbiology | | Dharmasena |
| | CMC Labeling | Liming Lu | |
| | RBPM | Kelly Ballard | |
| | ATL | Jun Liu | |
| | OPQA Review Chief | Maria-Teresa Gutierrez-Lugo | |
| **OPQ Issued Consults** | Not applicable | | |

## 2. Recommendation and Conclusion on Approvability

**Recommendation: Approval with PMCs/PMRs**

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761416 for ZIIHERA (zanidatamab-hrii) manufactured by (b) (4) . The data submitted in this application are adequate to support the conclusion that the manufacture of ZIIHERA (zanidatamab-hrii) 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:** (b) (4)
- **Drug Product:**
  - Manufacturing: (same as drug substance)
  - Labeling and secondary packaging: (b) (4)

### b. Fill size and dosage form:

300 mg of lyophilized powder in a single-dose vial

### c. Dating Period:

- **Drug Substance:**
  (b) (4) months at (b) (4) °C
- **Intermediate Substance, if applicable:** Not applicable
- **For packaged products:**
  - **Drug Product:** 24 months at 2-8°C
- **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.

d. Exempt from lot release:
- Yes
- ZIIHERA 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

**Three PMCs from OPQA III are listed below:**

1) To implement a two-tiered reference standard (RS) system consisting of primary and working RS (PRS and WRS), prior to the depletion of the current RS, through the submission of a prior approval supplement (PAS) per 21 CFR 601.12. Protocols including qualification of future PRS and WRS and requalification of PRS and WRS, should be included in the PAS.

   Final protocol submission date: 01/2025

2) To update the drug substance and drug product release and stability specifications for zanidatamab to include a validated C1q binding ELISA method with justified quantitative acceptance criteria, as a surrogate method to control the complement dependent cytotoxicity (CDC) activity. The updated specifications, method validation data, and other supporting information will be submitted to the BLA as a PAS per 21 CFR 601.12.

   Final report submission date: 06/2026

3) To develop, validate, and implement a test method for control of (b) (4) with justified quantitative acceptance criteria in the drug substance release specification for zanidatamab. The updated specification, method validation report, and any other supporting information will be submitted to the BLA as a PAS per 21 CFR 601.12.

   Final Report Submission: 03/2026

4. Basis for Recommendation

a. Summary:

Zanidatamab-hrii (also known as JZP598 and ZW25) is a humanized, bispecific, IgG1-like monoclonal antibody directed against the juxtamembrane extracellular domain (ECD4) and the dimerization domain (ECD2) of human epidermal growth factor receptor 2 (HER2). The ECD4 and ECD2 are the same domains that can be recognized by trastuzumab and pertuzumab, respectively. Binding of zanidatamab with HER2 induces formation of receptor clusters and receptor internalization resulting in reduced HER2 expression, leads to inhibition of growth factor-dependent and independent tumor cell proliferation, and potentially activates Fc-dependent effector functions, ADCC, CDC and ADCP. It is indicated for treatment of patients with HER2-positive, locally advanced (unresectable) or metastatic biliary tract cancer (BTC).

Four assays are used to control the potency of ZIIHERA (zanidatamab-hrii).

(b) (4)

.

The drug substance manufacturing process consists

(b) (4)

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. All facilities used for the

manufacture and quality control testing were found acceptable for the proposed operations. An on-site pre-licensing inspections (PLI) for the drug substance and drug product manufacturing facilities at (b) (4) and found satisfactory.

Results of the immunogenicity assays, the ADA and Nab assays, demonstrated that they were able to identify ADA and NAb positive individuals in post-treated samples, supporting the assay is fit-for-purpose. However, the risk of false-positive increases as the levels of soluble HER2 (sHER2) increase, which can over-estimate ADA positivity. OPQ recommends that the "treatment-emergent" definition is not used due to interference in pre-dose samples and that all post-treatment ADA samples above cut-point be considered positive to capture ADA positive status. After discussion with the clinical pharmacology review team, it was determined that they would like to request a PMC because of the impact to data interpretability with ADA false-positive.

The overall ZIIHERA (zanidatamab-hrii) 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 ZIIHERA (zanidatamab-hrii) 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 BLA is recommended for approval from the product quality, facility, microbiology and sterility assurance perspectives.

**b. Subdiscipline Recommendation:**

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

**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 ZIIHERA (i.e., there is no specific test method described in regulation for ZIIHERA that establishes an official standard of potency). We next considered whether potency is a factor for ZIIHERA 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 ZIIHERA for purposes of § 610.61(r) because lot variability is not a concern for ZIIHERA as ZIIHERA'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:

(b) (4)

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

(b) (4)

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.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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JUN LIU
10/31/2024 11:07:53 AM

MARIA T GUTIERREZ LUGO
10/31/2024 01:03:52 PM