CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761416Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 18, 2024

To: Rebecca Cohen, RN, MPH, OCN, Regulatory Health Project Manager, Division of Oncology 3 (DO3)

Doris Auth, PharmD, Associate Director for Labeling, DO3

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZIIHERA® (zanidatamab-hrii) for injection, for intravenous use

BLA: 761416

Background: In response to DO3's consult request dated July 2, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI) or Medication Guide (MG), and carton and container labeling for the original BLA submission for ZIIHERA® (zanidatamab-hrii) for injection, for intravenous use.

PI/(PPI or MG): OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 10, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/MG, and comments were sent under separate cover on October 17, 2024.

Carton and Container Labeling: OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on September 6, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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

---

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

/s/

REBECCA A FALTER
10/18/2024 08:18:07 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 17, 2024
To:	Rebecca Cohen Regulatory Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD, BCACP Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ZIIHERA (zanidatamab-hrii)
Dosage Form and Route:	for injection, for intravenous use
Application Type/Number:	BLA 761416
Applicant:	Jazz Pharmaceuticals Ireland Limited

1 INTRODUCTION

On December 23, 2023, Jazz Pharmaceuticals Ireland Limited, submitted for the Agency's review Biologics License Application (BLA) 761416 for ZIIHERA (zanidatamab-hrii) injection. This original BLA This NME is a HER2-directed bispecific antibody proposing an indication for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test. DO3 has designated this application as a Priority review.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology III (DO3) on September 10, 2024 and July 2, 2024 respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ZIIHERA (zanidatamab-hrii) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft ZIIHERA (zanidatamab-hrii) PPI received on December 23, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 10, 2024.
- Draft ZIIHERA (zanidatamab-hrii) Prescribing Information (PI) received on December 23, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 10, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

---

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

/s/

MARIA T NGUYEN
10/17/2024 03:10:40 PM
zaniadatam-hrii (ZIIHERA) BLA 761416 PPI

REBECCA A FALTER
10/17/2024 03:16:44 PM

LASHAWN M GRIFFITHS
10/17/2024 10:00:50 PM

Clinical Inspection Summary

Date	October 9, 2024
From	Courtney McGuire, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Vaibhav Kumar, MD, Clinical Reviewer Sandra Casak, MD, Clinical Team Leader Rebecca Cohen, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	BLA 761416
Applicant	Jazz Pharmaceuticals Ireland, Limited
Drug	Zanidatamab
NME (Yes/No)	Yes
Therapeutic Classification	HER2-directed bispecific antibody
Proposed Indication	Treatment of previously treated, unresectable locally advanced or metastatic HER2-positive biliary tract cancer (BTC), as detected by an FDA-approved test
Consultation Request Date	5/8/2024
Summary Goal Date	10/20/2024
Action Goal Date	11/20/2024
PDUFA Date	11/29/2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Jazz Pharmaceuticals Ireland, Limited, submitted clinical data from Study ZWI-ZW25-203 (NCT04466891) to the Agency in support of a Biological Licensing Application (BLA 761416) for zanidatamab. The proposed indication is for the treatment of adults with previously treated, unresectable locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)-positive biliary tract cancer (BTC), as detected by an FDA-approved test.

Two foreign clinical investigators (CIs), Drs. Kim and Choi, one domestic CI, Dr. Harding, the Sponsor, Jazz Pharmaceuticals Ireland, Limited, and the imaging contract research organization (CRO), (b) (4) were inspected.

The inspections of CIs, Dr. Choi and Dr. Harding, the imaging CRO ((b) (4) and Sponsor (Jazz) revealed no significant discrepancies or regulatory violations. The inspection of Dr. Kim identified 18 protocol deviations for omission of protocol required corticosteroid prophylaxis prior to IV infusion in 2 subjects. However, there were no associated infusion-related reactions, and the deviations do not appear to impact the overall reliability of safety or efficacy data for this site. Based on the inspection results of the 3 CIs, CRO, and Sponsor, the

data generated by the inspected CIs and the CRO, and submitted by the Applicant, Jazz, appear acceptable in support of the proposed indication.

II. BACKGROUND

On December 28, 2023, Jazz Pharmaceuticals Ireland Limited submitted BLA 761416 seeking approval of zanidatamab for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive BTC, as detected by an FDA-approved test.

Zanidatamab is a novel humanized, bispecific antibody that binds to the same 2 extracellular domains of HER2 as trastuzumab (ECD4) and pertuzumab (ECD2). Binding of zanidatamab results in blockade of ligand-dependent and independent growth and potent activation of antibody-dependent cellular cytotoxicity.

The primary evidence of efficacy for zanidatamab for the proposed indication and the focus of the BIMO inspections was a single phase 3 trial, Study ZWI-ZW25-203.

Study Design

Study ZWI-ZW25-203 was a phase 2b, multicenter, global, open-label, single-arm study of zanidatamab monotherapy in subjects with HER2-amplified, inoperable and advanced or metastatic BTC, including gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma. Following a 28-day screening period, eligible subjects enrolled into the following 2 cohorts based on HER2 status:

- Cohort 1: HER2 amplification by ISH and HER2 overexpression by IHC, i.e., IHC 2+ or 3+ (planned 75 subjects)
- Cohort 2: HER2 amplification by ISH and HER2 IHC 0 or 1+ (planned 25 subjects)

All enrolled subjects received intravenous zanidatamab every 2 weeks until unacceptable toxicity, disease progression (either radiographic progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) or unequivocal clinical progression), death, loss to follow-up, pregnancy, physician decision, or withdrawal of consent.

Endpoints

- *Primary endpoint*: Confirmed objective response rate (ORR) per RECIST 1.1, assessed by independent central review (ICR), evaluated in the Cohort 1 Primary Efficacy Analysis set.

- *Key secondary efficacy endpoints*: Duration of Response (DOR), Overall survival, Progression-free survival (PFS)

The final analysis of efficacy was based on blinded independent central review (BICR) of tumor scans.

Study Status
As of the data cut-off of July 28, 2023, the study enrolled the following subjects across 32 study centers, across countries in Asia, Europe, North America, and South America, including 17 subjects enrolled across 5 sites in US.

Safety population: N = 87 (total)
Cohort 1: N=80
Cohort 2: N=7

Efficacy population: N = 80 (Primary Efficacy Analysis Set, Cohort 1)

Dr. James Harding (Site 0109), Dr. Jin W Kim (Site 0302), Dr. Hye J Choi (Site 0306), the Sponsor (Jazz Pharmaceuticals Ireland, Limited), and the imaging CRO ((b) (4) were inspected.

RESULTS

1. **James Harding (Site 0109, Study ZWI-ZW25-203)**
   Memorial Sloan Kettering Cancer Center (MSKCC)
   633 Third Avenue
   New York, NY 10017
   USA

Inspection Dates: July 12, 2024, to July 19, 2024

This investigator was inspected as a routine PDUFA inspection for Study ZWI-ZW25-203. This was the first FDA inspection for this investigator.

The site consented and screened a total of 31 subjects, of which 8 were enrolled and randomized at the site. The study is closed to enrollment.

The inspection reviewed subject-related source documents including informed consent forms (ICFs) and eligibility checklists for all 31 screened subjects, and the following for the 8 enrolled subjects: medical history, lab results, physical examinations, vital signs, adverse events (AEs), concomitant medications, visit records, and clinical assessments. All available source documents were located in the MSKCC Electronic Medical Record (EMR), including subject-source records created directly within the EMR as well as certified copies of paper records.

Reviewer comment. The site's approach to maintaining source documents, including the MSKCC Standard Operating Procedures (SOPs) for Source Documentation and Medical Record Integrity, appear compliant with 21 CFR 11.

The inspection also reviewed the following study-related documents: Institutional Review

Board (IRB) correspondence and approvals (initial, continuing reviews, amendments), study protocol and amendments, regulatory documents, Form 1572s, Delegation of Authority logs, financial disclosures, curriculum vitae (CV), informed consent documents, investigational product (IP) storage and accountability records, training and monitoring records, monitoring records, and lab manuals and certifications.

Imaging scans supporting the primary endpoint appeared to be performed according to protocol, including submission to the imaging CRO for BICR. There was no evidence of under-reporting of AEs or protocol violations based on source data reviewed.

Based on the results of the inspection, Study ZWI-ZW25-203 data generated at Dr. Harding's site appear acceptable in support of the proposed indication in the BLA.

2. Dr. Jin Won Kim (Site 0302, Study ZWI-ZW25-203)
Seoul National University Bundang Hospital, Beon-Gil, Bundang
173 82 Gumi-Ro
Seongnam, Gyeonggi, 13620
South Korea

Inspection Dates: July 15, 2024, to July 19, 2024

This investigator was inspected as a routine PDUFA inspection for Study ZWI-ZW25-203. The last inspection occurred in 2022; there were no significant findings.

There were 11 subjects screened and 9 subjects enrolled and treated with IP. All 9 subjects discontinued from the study.

The inspection reviewed subject-related source documents including ICFs for all 11 screened subjects, and the following for the 9 enrolled subjects: progress notes, laboratory tests, infusion records, and questionnaires. Subject-related records were reviewed in the EMR, paper study binders, and electronic case report forms (eCRF).

Study-related records reviewed included, but were not limited to Clinical Trial Agreements, study staff qualifications and training, financial disclosures, ICFs, Site Signature and Delegation of Responsibilities Log, IRB approvals, Sponsor and CRO monitoring records, other study records (e.g., administrative study files, correspondence files, master subject list, screening lists), IP accountability / disposition / labeling, and records retention.

Radiographic scans and related investigator assignments supporting the primary and key secondary efficacy endpoints were performed as specified in the protocol, and consistent with the data submitted to the BLA. All radiographic scans were submitted to the imaging CRO for BICR. Subject survival status was verified in the site EMR and consistent with data line listings.

There was no evidence of under-reporting of AEs based on source data reviewed.

The inspection identified recurrent, reported protocol deviations for inadequate premedication prior to IP administration (Protocol Section 5.2.7.1).

Reviewer comment. Between March 9, 2021, and August 10, 2021, there were 18 protocol deviations involving 2 subjects for omission of protocol required corticosteroid pretreatment. Dr. Kim omitted the corticosteroid pretreatment out of concern for corticosteroid-related side effects, however, he did not obtain Sponsor's permission to alter the regimen which was required by the protocol. Following monitoring visits, on August 23, 2021, Dr. Kim submitted and received Sponsor approval to administer a reduced dosage of corticosteroids. During the inspection, Dr. Kim expressed an understanding of the finding and committed to informing the medical monitor and/or Sponsor before changing any protocol requirements. From a safety perspective, no infusion-related reactions appear associated with these protocol deviations. While the protocol deviations did not appear to impact the interpretation of safety or efficacy for either subject, the recurrent nature of events and Dr. Kim's failure to obtain Sponsor preapproval for the alternative regimen, suggest a lack of adherence to the protocol on the part of Dr. Kim.

The inspection also identified multiple recurrent, unreported deviations for drug reconstitution errors.

Reviewer comment. The Pharmacy Manual- (b) (4) *instructions state to "Allow vial to reconstitute for around 10 minutes" and additional FAQs indicate "6 to 10 minutes is to be followed." The Interim Medical Monitoring Visit Follow-up Report dated October 27, 2023 (i.e., after July 28, 2023, data cutoff), retrospectively identified approximately 100 protocol deviations for drug reconstitution times outside the required range (i.e., too short [2 to 5 min.], or too long [11 to 24 min.]) between December 15, 2020, and January 11, 2022. The deviations impacted all subjects at the site (1 to 46 per subject, mean of 11). A CAPA was initiated that included pharmacist training and IRB reporting. While the protocol deviations were not documented with the BLA submission, OSI notes the reconstitution errors are unlikely to impact drug product quality or patient safety based on the known IP stability (i.e., up to 4 hours at ambient conditions), and the minimum of the historical range for reconstitution time* (b) (4) *per BLA 761416, Section 3.2.P.2.3, Manufacturing Process Development, Figure 51).*

Based on the results of the inspection, the data generated at Dr. Kim's site appear acceptable in support of the proposed indication in the BLA.

3. Dr. Hye J. Choi (Site 0306, Study ZWI-ZW25-203)
50-1, Yeonse-Ro
Seodaemun, Seoul, 03722
South Korea

Inspection Dates: July 22, 2024, to July 25, 2024

This investigator was inspected as a routine PDUFA inspection for Study ZWI-ZW25-203. This was the first FDA inspection for this investigator.

There were 14 subjects screened and 9 subjects randomized and treated with IP. Nine subjects discontinued from the study.

The inspection reviewed subject-related source documents including ICFs for all 14 screened subjects, and the following for the 9 enrolled subjects: progress notes, laboratory tests, infusion records, and questionnaires. Subject-related records were reviewed in the EMR, paper study binders, and the eCRF.

Study-related records reviewed included ICFs forms, protocol and amendments, IRB approvals, financial disclosures, Clinical Trial Agreement, Delegation Log, study staff qualification and training, monitoring visits and reports, IP accountability / storage / disposition, administrative study files, correspondence files, master subject list, screening lists, and safety reports.

Radiographic scans and related investigator assignments supporting the primary and key secondary efficacy endpoints were performed as specified in the protocol, and consistent with the data submitted to the BLA. All radiographic scans were submitted to the imaging CRO for central review. Subject survival status was verified in the site EMR and consistent with data line listings.

There was no evidence of under-reporting of AEs or protocol violations based on source data reviewed. There were no incomplete and/or inaccurate records, or evidence of data fabrication.

Based on the results of the inspection, the data generated at Dr. Choi's site appear acceptable in support of the proposed indication in the BLA.

4. Jazz Pharmaceuticals, Inc. (Study ZWI-ZW25-203)
2005 Market St Ste 2100
Philadelphia, PA, 19103-7002
USA

Inspection dates: July 9, 2024, to July 15, 2024.

Jazz Pharmaceuticals was inspected at their US location as a routine PDUFA inspection for Study ZWI-ZW25-203. The most recent inspection of Jazz Pharmaceuticals was conducted in February 2024; there were no significant findings.

Study documents reviewed during the inspection included, but were not limited to, organizational charts, SOPs, vendor contract and service agreements, ZWI-ZW25-203 study documents, site training, qualifications and documentation of medical monitors, safety monitoring, control of IP, financial disclosures, Independent Data Monitoring Committee charter and communications, and electronic systems for data collection and handling.

For 6 clinical sites (0105, 0302, 0303, 0306, 0407, and 0903), the inspection reviewed site monitoring visit reports, Sponsor correspondences, Investigator Agreements, data from serious adverse event logs, protocol deviation logs, and IP accountability records. The protocol deviation log identified a total of 18 protocol deviations across 2 subjects at Dr. Kim's site

(0302) for "Pretreatments were not administered per protocol."

> *Reviewer comment. Dr. Kim omitted protocol required prophylactic corticosteroid treatment for potential infusion reactions due to safety concerns with the corticosteroid dosage. The medical monitor addressed these protocol deviations during multiple monitoring visits, including CI retraining and reenforcing the importance of Sponsor preapproval for an alternative premedication regimen per Protocol Section 5.2.7.1. On August 23, 2021, the Sponsor approved Dr. Kim's request for a reduced dose of corticosteroids. The Sponsor oversight and monitoring appears adequate. For additional details, refer to CI Inspection for Dr. Jin Won Kim (Site 0302/ ZWI-ZW25-203).*

Based on the results of the inspection, Jazz Pharmaceutical's oversight of the study and monitoring of the clinical investigators appear adequate.

5. (b) (4) **(Study ZWI-ZW25-203)** (b) (4)

Inspection dates: (b) (4)

(b) (4) was inspected as a routine PDUFA inspection for Study ZWI-ZW25-203. The firm was previously inspected in (b) (4), and there were no regulatory or GCP deviations observed.

This inspection reviewed (b) (4) responsibilities to perform an independent central imaging review for Study ZWI-ZW25-203, which included collection, medical assessment, and project management of imaging data. Records reviewed included the firm organizational chart, firm history, written procedures, quality assurance activities, training, reader qualifications, financial conflicts of interest, outsourced services, contacts / agreements with sponsors / CROs, communication plans, record retention, electronic systems and validations, and blinding activities. (b) (4) data collection and handling procedures, data transfer, adherence to the protocol and Independent Review Charter, and adjudication procedures were also reviewed and found to be adequate.

The inspection verified the primary efficacy endpoint for 35 efficacy responders by comparison of tumor diameter measurements and tumor response/progression results in the source records with data line listings at all time points, inclusive of the 4-week objective response confirmation. There were no discrepancies identified. Table 1 lists the subjects whose tumor measurements were verified:

Table 1. Unique Subject IDs for Verified Measurements

(b) (6)

Based on the results of the inspection, the imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the BLA.

{See appended electronic signature page}

Courtney McGuire, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Review Division/ Division Director / Steven Lemery
Review Division/Project Manager/ Rebecca Cohen
Review Division/Clinical Team Lead/ Sandra Casak
Review Division/Clinical Reviewer/ Vaibhav Kumar
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

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

/s/

COURTNEY S MCGUIRE
10/09/2024 09:20:33 AM

MICHELE B FEDOWITZ
10/09/2024 09:24:36 AM

JENN W SELLERS
10/09/2024 09:33:36 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 24, 2024
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761416
Product Name, Dosage Form, and Strength:	Ziihera (zanidatamab-xxxx)[a] for injection, 300 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Jazz Pharmaceuticals Ireland Limited
FDA Received Date:	March 29, 2024
TTT ID #:	2024-8915
DMEPA 2 Safety Evaluator:	Ngoc-Linh Do, PharmD
DMEPA 2 Acting Team Leader:	Tingting Gao, PharmD

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder established zanidatamab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 INTRODUCTION

As part of the approval process for Ziihera (zanidatamab-xxxx) for injection, the Division of Oncology 3 (DO3) requested that we review the proposed Ziihera Prescribing Information (PI), Patient Package Insert (PPI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761416.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

The proposed Ziihera Prescribing Information (PI), container label, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 3 (DO3) in Section 4 and for Jazz Pharmaceuticals Ireland Limited in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Highlights of Prescribing Information
    a. Delete the text (b) (4) to reduce redundancy (b) (4)
    b. We recommend deleting the (b) (4) to reduce clutter and to increase prominence of the recommended dosage information.
2. Section 2 Dosage and Administration
    a. For Section 2.2, consider revising "30-60 minutes" to "30 to 60 minutes" for clarity.
    b. For Section 2.3, delete the text "((b) (4))" to reduce redundancy.

    In addition, we recommend moving Table (b) (4) Recommended Infusion Durations of [TRADENAME] to the Administration subsection in Section

2.5, since the infusion duration information is more appropriate in that subsection.

c. For Section 2.5, under the Reconstitution subheading, we recommend the following revisions to reduce clutter:

   i. Delete the statement [redacted].

   ii. Delete the statement [redacted]".

   iii. For the third bullet, deleted "[redacted]" so that it reads, "Reconstitute each 300 mg [TRADENAME] vial with 5.7 mL of Sterile Water for Injection. Slowly [redacted] direct the stream toward the inside wall of the vial, to obtain a final concentration of 50 mg/mL in an extractable volume of 6 mL.

   iv. Revise the bulletin regarding storage of reconstituted solution to "Use the reconstituted [TRADENAME] solution immediately [redacted] store the reconstituted [TRADENAME] solution at room temperature (18°C to 24°C [64°F to 75°F]) or in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 4 hours."

d. For Section 2.5, under the Dilution subheading, we recommend the following revisions for clarity.

   i. Revise the established names for the compatible diluents so that they are presented using the following USP monograph titles (e.g., 0.9% Sodium Chloride Injection or 5% Dextrose Injection).

   ii. Revise the concentration range so that it is spelled out as "0.4 mg/mL to 6 mg/mL". We recommend ensuring the unit of measure follows each numeric value for clarity and avoid using trailing zeros to minimize confusion.

   iii. We recommend revising the terms "[redacted]" and "[redacted]", and "diluted [TRADENAME] solution" to "infusion solution" for consistency.

   iv. Revise the bulletin regarding storage of diluted solution to "Use the infusion solution of [TRADENAME] immediately upon dilution. [redacted] store the infusion solution at room temperature (18°C to 24°C [64°F to 75°F]) for up to 12 hours [redacted], or in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours [redacted]"

v. We recommend spell out the abbreviation “IV” to “intravenous” for clarity.

e. The infusion durations information is missing in the Administration subsection. We recommend moving Table (b) (4) Recommended Infusion Durations of [Trade Name] to this subsection since the infusion duration information is more appropriate in the Administration subsection.

f. We defer to OPQ to whether Section 2.6 is needed as similar information is included in the relevant subsections (Reconstitution and Dilution Subsection).

3. Section 3 Dosage Forms and Strengths

a. Delete the text “(b) (4)” as that information is not required in this section.

5 RECOMMENDATIONS FOR JAZZ PHARMACEUTICALS IRELAND LIMITED

A. General Comments (Container Label(s) and Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholder “TRADENAME”. We reference our June 17, 2024, Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Ziihera, was found conditionally acceptable. We recommend replacing the placeholder “TRADENAME” with the conditionally acceptable proprietary name, Ziihera, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.

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

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

2. Revise the dosage statement to "Recommended Dosage: See Prescribing Information" to align with the current terminology in the PI.

A. Container Label(s)

1. The discard statement "Discard unused portion" is not present. Inclusion of this discard statement helps minimize the risk of the entire contents of the vial being given as a single dose. We recommend adding the statement "Discard Unused Portion" next to "Single-Dose Vial" to read as "Single-Dose Vial. Discard Unused Portion". See *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)*.

B. Carton Labeling

1. 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). (b) (4)

   Recommend relocating the strength statement "300 mg/vial" so that it is immediately located below the proprietary name, nonproprietary name, and dosage form "for injection" on the PDP of the carton to facilitate proper identification of the product.

2. Revise the package type term to remove the word "(b) (4)" so that the statement reads "Contains 2 single-dose vials. Discard unused portion."

3. To improve readability of the information on the side panel, separate out the resultant concentration information as a new paragraph. See example below:

   > Each single-dose vial of reconstituted product contains 300 mg of zanidatamab-xxxx and the inactive ingredients: polysorbate 20 (0.63 mg), sodium succinate (4.3 mg) succinic acid (4.3 mg), and sucrose (567 mg).
   >
   > (b) (4) Reconstitute with 5.7 mL of Sterile Water for Injection to obtain a concentration of 50 mg/mL.

   We recommend revising the established name for the compatible diluent so that it is presented using the USP monograph titles (e.g., Sterile Water for Injection). Additionally, consider deleting the statement "(b) (4) " since the route of administration is already stated on the principal display panel.

4. As currently presented, the product identifier is missing a placeholder for the machine-readable, 2D data matrix barcode format. Ensure the 2D data matrix barcode is included as part of the product identifier. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Ziihera received on March 29, 2024 from Jazz Pharmaceuticals Ireland Limited.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Ziihera</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Nonproprietary Name</td><td>zanidatamab-xxxx</td></tr>
<tr><td>Indication</td><td>for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive biliary tract cancer, as detected by an FDA-approved test</td></tr>
<tr><td>Dosage Form</td><td>for injection</td></tr>
<tr><td>Strength</td><td>300 mg/vial</td></tr>
<tr><td>Route of Administration</td><td>Intravenous infusion</td></tr>
<tr><td>Dose and Frequency</td><td>20 mg/kg intravenously once every 2 weeks until disease progression or unacceptable toxicity.
The recommended infusion durations are as follows:
<table>
<tr><th>Dose</th><th>Infusion Duration</th></tr>
<tr><td>First and Second</td><td>120-150 minutes</td></tr>
<tr><td>Third and Fourth</td><td>90 minutes, if previous infusions were well-tolerated</td></tr>
<tr><td>Subsequent</td><td>60 minutes, if previous infusions were well-tolerated</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>It is supplied as a sterile, preservative free, white lyophilized powder in a single-dose vial. Each single-dose vial (NDC 68727-950-01) contains 300 mg zanidatamab-xxxx. Each carton (NDC 68727-950-02) contains 2 single-dose vials.</td></tr>
<tr><td>Storage</td><td>Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton until time of reconstitution. Do not freeze.</td></tr>
<tr><td>Container Closure</td><td>The container closure consists of a vial (a clear, Type (b) (4) (b) (4) glass), a stopper (a 20 mm (b) (4) and an overseal (20 mm, flip-off, aluminum overseal with (b) (4) plastic button)</td></tr>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Ziihera labels and labeling submitted by Jazz Pharmaceuticals Ireland Limited.

- Prescribing Information and Patient Package Insert received on March 29, 2024, available from \\CDSESUB1\EVSPROD\bla761416\0006\m1\us\uspi.docx
- Container label(s) received on March 29, 2024
- Carton labeling received on March 29, 2024

B.2 Container Label(s) and Carton Labeling Images

Container label(s)

(b) (4)

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

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

NGOC - LINH DO
07/24/2024 10:47:46 AM

TINGTING GAO
07/24/2024 10:49:20 AM