NDA 213702/S-008

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSMARKETING
REQUIREMENT/COMMITMENT

Jazz Pharmaceuticals Ireland Ltd.
Attention: Jonas Wilf, MMH, RAC
Senior Director, Global Regulatory Lead
One Commerce Square
2005 Market Street, Suite 2100
Philadelphia, PA 19103

Dear Jonas Wilf:

Please refer to your supplemental new drug application (sNDA) dated January 31, 2023, received January 31, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zepzelca (lurbinectedin).

This Prior Approval sNDA provides for the following changes to the US Prescribing Information:

- Updates to DOSAGE AND ADMINISTRATION section (revised subsection *2.2 Dosage Modifications for Adverse Reactions*, and addition of subsection *2.3 Dosage Modifications for Use with Strong CYP3A Inhibitors*).
- Revisions to DRUG INTERACTION (section 7) to include information on coadministration of Zepzelca with CYP3A strong inhibitors, moderate inhibitors, and strong inducers.
- Update to CLINICAL PHARMACOLOGY (subsection *12.3 Pharmacokinetics*) to include pharmacokinetic information from drug-drug interaction studies.
- Formatting and editorial changes throughout the Full Prescribing Information, with corresponding changes to the Patient Package Insert.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

We acknowledge your January 31, 2023, submission containing final printed carton and container labeling.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FULFILLMENT OF POSTMARKETING REQUIREMENT/COMMITMENT

We have received your submissions dated July 15, 2022, and October 21, 2022, containing the final reports for the following requirement and commitment listed in the June 15, 2020 approval letter.

3831-4 Submit the final report and datasets from a clinical pharmacokinetic trial to assess the potential effects of Itraconazole on lurbinectedin in patients with advanced solid tumors and determine the magnitude of increase exposure and appropriate dosage recommendation of lurbinectedin when administered concomitantly with strong CYP3A inhibitors, that may inform product labeling. This trial should be designed and conducted in accordance with the FDA Guidance for Industry, titled; "*Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications*."

3831-6 Submit the final report from a clinical trial to evaluate the effect of repeat doses of a moderate CYP3A inducer on the single dose pharmacokinetics of lurbinectedin and to determine the magnitude of decrease in lurbinectedin exposure, and appropriate dosage recommendation when lurbinectedin is coadministered with moderate CYP3A inducers, that may inform product labeling. Designed the trial in accordance with the FDA Guidance for Industry, titled "*Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implication*".

We have reviewed your submission and conclude that the above requirement and commitment were fulfilled.

We remind your that there are postmarketing requirements listed in the June 15, 2020 approval letter and October 24, 2022, postapproval postmarketing requirement letter that are still open.

We remind your that accelerated approval PMR 3831-7 and PMR 3831-8 listed in the October 24, 2022, postapproval postmarking requirement letter are still open. Pursuant to 21 CFR 314-510 (Subpart H), continued approval of the drug is contingent upon verification and description of clinical benefit and completion of the clinical trial for PMR 3831-7 and PMR 3831-8.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Jeffrey Ingalls, Regulatory Health Project Manager, at 301-796-4444 or via email at Jeffrey.ingalls@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, MD
Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

ERIN A LARKINS
07/28/2023 12:46:36 PM
Supervisory Associate Director, DO2 as designated signatory authority for Dr. Harpreet Singh