CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213702Orig1s000

Trade Name:	Zepzelca
Generic or Proper Name:	lurbinectedin
Sponsor:	Pharma Mar USA, Inc.
Approval Date:	June 15, 2020
Indication:	For the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after prior platinum-based chemotherapy.

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213702Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	**X**
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 213702

ACCELERATED APPROVAL

Pharma Mar USA, Inc.
Attention: Sonia Vela
Project Leader
205 East 42nd Street
Suite 15003
New York, NY 10017

Dear Ms. Vela:

Please refer to your new drug application (NDA) dated and received December 16, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zepzelca (lurbinectedin), injection, for intravenous use.

This new drug application provides for the use of Zepzelca (lurbinectedin) injection, 4 mg lyophilized powder in a single-dose vial for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after prior platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information and Patient Package Insert). 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 via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on June 12, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213702**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Zepzelca was not referred to an FDA advisory committee because this drug is not the first in its class, and the application did not raise significant safety or efficacy issues; and the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated May 21, 2020. This requirement, along with required completion dates, is listed below.

3831-1 Submit the final report and datasets for the overall survival and progression-free survival analysis as determined by an Independent Review Committee from a clinical trial to confirm the clinical benefit of lurbinectedin in small cell lung cancer that may inform product labeling.

[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.

This could be from the Study titled, “Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin Versus Cyclophosphamide, Doxorubicin and Vincristine (CAV) or Topotecan as Treatment in Patients With Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS)”.

Final Protocol Submission:	05/2016 (completed)
Trial Completion:	02/2020 (completed)
Final Report Submission (OS):	02/2021

Submit clinical protocols to your IND 127944 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s)**.”

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of elevated drug levels and to determine appropriate dosage adjustment of lurbinectedin when administered concomitantly with moderate CYP3A inhibitors.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3831-2 Submit the final report of a physiologically-based pharmacokinetic modeling with the results from the drug interaction trial with a strong CYP3A4 inhibitor, to assess the effect of concomitant administration of a moderate CYP3A inhibitor on lurbinectedin exposure, that will determine the magnitude of increase in the exposure of lurbinectedin and appropriate dosage recommendation for patients receiving concomitant medications that are moderate CYP3A inhibitors, that may inform labeling. Design and conduct the trial in accordance with the FDA Guidance for Industry titled; "*Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications*."

The timetable you submitted on May 21, 2020 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 07/2021
Study Completion: 10/2024
Final Report Submission: 10/2024

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of elevated drug levels in the presence of mild, moderate, or severe hepatic impairment and to determine appropriate dose adjustment when lurbinectedin is used concomitantly with strong CYP3A inhibitors.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3831-3 Submit the analysis and datasets with the final report from a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of lurbinectedin in patients with mild, moderate, or severe hepatic impairment and determine the magnitude of increase exposure and appropriate dosage recommendations, that may inform product labeling. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

The timetable you submitted on May 21, 2020 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/2020
Trial Completion: 03/2025
Final Report Submission: 09/2025

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*."

The timetable you submitted on May 21, 2020 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/2020
Trial Completion: 12/2023
Final Report Submission: 06/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your (b) (4) with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3831-5 Submit the final analysis of overall response rate and duration of response along with the datasets for the small cell lung cancer cohort enrolled in study PM1183-B-005-14 titled; "*Clinical Trial of Lurbinectedin in Selected Advanced Solid Tumors*" to provide additional long-term efficacy data that may inform product labeling.

The timetable you submitted on May 21, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/2015 (completed)
Trial Completion: 11/2020
Final Report Submission: 05/2021

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"*.

The timetable you submitted on May 21, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2020
Trial Completion: 01/2024
Final Report Submission: 07/2024

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 127944 (b) (4) for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[4]

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[5]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Kwadwo Korsah, Pharm.D., Regulatory Health Project Manager, at (301) 796-6630.

Sincerely,

{See appended electronic signature page}

Marc Theoret, M.D.
Deputy Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

[5] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

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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.

/s/

MARC R THEORET
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