CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213702Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 11, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 213702
Product Name and Strength:	Zepzelca (Lurbinectedin) For Injection, 4 mg/vial
Applicant/Sponsor Name:	Pharma Mar USA Inc.
OSE RCM #:	2019-2596-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label and carton labeling received on June 10, 2020 for Zepzelca. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Zepzelca (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Stewart J. Label and Labeling Review for Zepzelca (NDA 213702). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 08. RCM No.: 2019-2596.

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/s/

JANINE A STEWART
06/11/2020 09:08:38 AM

CHI-MING TU
06/11/2020 12:33:35 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	June 8, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 213702
Product Name, Dosage Form, and Strength:	Zepzelca (Lurbinectedin) For Injection, 4 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pharma Mar USA Inc.
FDA Received Date:	May 29, 2020, and June 8, 2020
OSE RCM #:	2019-2596
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the review process for this NDA, this review evaluates the proposed Zepzelca (Lurbinectedin) prescribing information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of materials found that the proposed Zepzelca PI, container label, and carton labeling may be improved to promote safe use of this product. Thus, we provide related recommendations below in Section 4.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Zepzelca PI and container label can be improved to increase the clarity, and to promote the safe use of the product. We provide recommendations for DO2 in Section 4.1 and recommendations for Pharma Mar USA Inc. in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. In Table 1: *Dose Reduction for TRADENAME for Adverse Reactions*, the dosage recommended for a first and second dose reduction is expressed with an interval of (b) (4) Revise the dosing interval for consistency with the dosing interval stated in Section 2.1 *Recommended Dosage* as "every 21 days".

4.2 RECOMMENDATIONS FOR PHARMA MAR USA INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container label & Carton Labeling)

1. To present the customary order of product information and for consistency between the container label and carton labeling, consider relocating the strength statement to appear immediately under the established name. As currently presented, the container label presents the strength under the proprietary and established names, but the carton labeling presents the strength to the right of the proprietary and established names.
2. Revise the statement "Store (b) (4) at 2°C to 8°C (36°F to 46°F)" to read "Store refrigerated at 2°C to 8°C (36°F to 46°F)". We recommend this to simplify the statement, to increase the prominence of this important information, and to minimize the risk of the storage information being overlooked.
3. Revise the "(b) (4)" statement to read "Caution: Cytotoxic agent" and consider presenting it in a (b) (4) font color to increase its prominence.
4. Consider unbolding the "Rx only" statement to allow visual prominence for other statements.
5. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Container Label

1. Consider and evaluate if the proposed container is too small and the legibility of text presented on the container label. Please note for drug packaged in a container too small or unable to accommodate a label with sufficient space, the container label must include at minimum the product's proprietary name (if any), the established name; product strength; lot number; and the name of the manufacturer, packer, or distributor provided that all required information is present on the carton labeling or in the prescribing information per 21 CFR 201.10(i). USP requires the label of an official drug product to bear an expiration date. As currently described in your submission, the container label size is (b) (4) .

   If your proposed product is not packaged in a container too small, then add a usual dosage statement to read "Recommended Dosage: See prescribing information."

2. Revise the presentation of the strength statement from displaying on two lines to one line as "4 mg per vial". As currently presented, there is a lot of space after the "4 mg" on the first line, making it seems like there is something truncated between the words "4 mg" and "per vial".

3. Relocate and revise the statements "(b) (4)" and "(b) (4) " statements to read "Single-Dose Vial. Discard unused portion." for consistency with the carton labeling. Additionally, consider relocating the statement "Single-Dose Vial. Discard unused portion" to the principal display panel (PDP).

4. Consider relocating the statement "For Intravenous Infusion Only" statement to appear on the PDP.

C. Carton Labeling

1. Important product information on the back panel appears cluttered. To reduce redundancy and clutter, and to improve readability on the back panel:

   a. Merge the statements "(b) (4) ..." and "(b) (4) ..." to read "Reconstitute with 8 mL of Sterile Water for Injection, USP to achieve a solution containing 0.5 mg/mL lurbinectedin."
   b. Revise the statement "... (b) (4) ..." to read "Must be further diluted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection."
   c. Consider revising the statement "(b) (4) ..." to read "Must be infused within 24 hours of preparation".

d. Delete the statement “Discard unused portion”. This information already appears on the principal display panel (PDP).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zepzelca (Lurbinectedin) received on June 8, 2020 from Pharma Mar USA Inc..

Table 2. Relevant Product Information for Zepzelca (Lurbinectedin)	
Initial Approval Date	N/A
Active Ingredient	lurbinectedin
Indication	For the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.
Route of Administration	Intravenous infusion
Dosage Form	For Injection
Strength	4 mg/vial
Dose and Frequency	The recommended dose is 3.2 mg/m^2 by intravenous infusion over 60 minutes (b) (4) every 21 days until disease progression or unacceptable toxicity.
How Supplied	Single-dose vials individually packaged in cartons containing 1 vial
Storage	Store refrigerated at 2°-8°C (36°-46°F).
Container Closure	20 mL, 20 mm USP (b) (4) clear glass vial with 20 mm gray stopper sealed with a blue flip-off cap.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Zepzelca (Lurbinectedin) labels and labeling submitted by Pharma Mar USA Inc..

- Container label received on May 29, 2020
- Carton labeling received on May 29, 2020
- Prescribing Information (Image not shown) received on June 8, 2020 available from \\cdsesub1\evsprod\nda213702\0035\m1\us\draft-non-annotated-labeling-tracked.docx

G.2 Label and Labeling Images

(b) (4)

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

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/s/

JANINE A STEWART
06/08/2020 12:49:10 PM

CHI-MING TU
06/08/2020 12:52:51 PM

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

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

Memorandum

Date: May 12, 2020

To: Kwadwo Korsah, PharmD, MS
Regulatory Project Manager
Division of Oncology 2 (DO2)

From: Nazia Fatima, PharmD, MBA, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (lurbinectedin) for injection

NDA: 213702

In response to DO2 consult request dated January 14, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original NDA TRADENAME (lurbinectedin) for injection.

OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DO2 on April 30, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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/s/

NAZIA FATIMA
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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:	May 12, 2020
To:	Kwadwo Korsah, PharmD, MS Regulatory Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatimza, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (lurbinectedin)
Dosage Form and Route:	for injection
Application Type/Number:	NDA 213702
Applicant:	Pharma Mar USA, Inc.

1 INTRODUCTION

On December 16, 2019, Pharma Mar USA, Inc., submitted for the Agency's review an original New Drug Application (NDA) 213702 for TRADENAME (lurbinectedin) for injection with the proposed indication for the treatment of patients with small cell lung cancer SCLC) (b) (4).

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 II (DO2) on January 14, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (lurbinectedin) for injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (lurbinectedin) for injection PPI received on December 16, 2019, and received by DMPP and OPDP on April 30, 2020.
- Draft TRADENAME (lurbinectedin) for injection Prescribing Information (PI) received on December 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 30, 2020.

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%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

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.

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/s/

SUSAN W REDWOOD
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05/12/2020 03:53:58 PM

SHARON R MILLS
05/12/2020 04:05:22 PM

LASHAWN M GRIFFITHS
05/12/2020 07:40:02 PM

Clinical Inspection Summary

Date	5/12/2020
From	Michele Fedowitz, M.D., Yang-Min (Max) Ning, M.D., Ph.D. Kassa Ayalew, M.D., M.P.H. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Sonia Singh, M.D. Adnan Jaigirdar, M.D. Harpreet Singh, M.D Division of Oncology 2 (DO2) Office of Oncologic Diseases (OOD)
NDA #	213702
Applicant	Pharma Mar USA, Inc.
Drug	Lurbinectedin
NME (Yes/No)	Yes
Therapeutic Classification	(b) (4)
Proposed Indication	Treatment of patients with small cell lung cancer (SCLC)
Consultation Request Date	1/14/2020
Summary Goal Date	6/1/2020
Action Goal Date	6/12/2020
PDUFA Date	8/16/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from a single-arm trial, Study PM1183-B-005-14, was submitted to the Agency in support of a New Drug Application (NDA 213720) for lurbinectedin for the treatment of patients with small cell lung cancer (SCLC) (b) (4) The study sponsor, Pharma Mar Inc., and the contract research organization (CRO), (b) (4) as well as 2 clinical investigators of the study, Dr. Jose Manuel Trigo (Site ES022) and Dr. Sant Chawla (Site US013) were selected for audit.

The inspections of Dr. Trigo and the CRO (b) (4) showed that the Applicant's submitted clinical data were verifiable, with no evidence of underreporting of adverse events or insufficient protection of study subjects. The scheduled inspections of Dr. Chawla and the study sponsor, Pharma Mar Inc., were cancelled because of the COVID-19 pandemic which has significantly limited OSI's ability to conduct onsite Good Clinical Practice (GCP) inspections. (see additional information in the Results section of this summary).

Based on the results of these completed inspections, the conduct of this study was adequately

monitored, and the clinical data generated from Dr. Trigo's site appear to be reliable in support of this NDA.

II. BACKGROUND

The Applicant, Pharma Mar USA Inc., seeks accelerated approval for lurbinectedin for the treatment of patients with small cell lung cancer (SCLC) (b) (4) . Lurbinectedin is an inhibitor of oncogenic transcription and its investigational name is PM01183 studied under IND 127944 in SCLC.

To support the proposed indication for lurbinectedin in this NDA, the applicant submitted clinical data from Study PM1183-B-005-14, titled, "A Multicenter Phase II Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors." Efficacy data from a cohort of 105 subjects with SCLC is the basis for this NDA.

This study (NCT02454972) is an ongoing, multicenter, open-label, non-comparative, phase 2 trial designed to assess the efficacy and safety of lurbinectedin in subjects with multiple advanced solid tumors, including SCLC. Subjects in the SCLC cohort were required to have pathologically proven diagnosis of small cell lung cancer, measurable disease as defined by RECIST v 1.1, and to have documented progression following prior platinum-containing therapy. The primary efficacy endpoint was confirmed overall response rate (ORR) per the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 according to the Investigator assessment (IA). The ORR assessment, confirmed by a blinded Independent Review Committee (IRC), was included as a secondary objective for the SCLC cohort.

Subjects received lurbinectedin as a single agent dosed at 3.2 mg/m^2 every 3 weeks until disease progression, unacceptable toxicity (including a protocol deviation affecting the risk/benefit profile for the subject), treatment delay > 3 weeks, non-compliance, refusal, or investigator's decision. Tumor assessments were to be performed with CT or MRI scans at baseline and every two cycles ± 7 days until Cycle 6, and thereafter every three cycles.
From October 16, 2015 through January 15, 2019 (the data cutoff date for the interim analysis in this NDA), the study enrolled 345 subjects from 9 countries, including Belgium, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, and the United States (U.S.). Of them, 23% were from the U.S. The SCLC cohort had 105 subjects enrolled, with 10% from the U.S. Enrollment for the SCLC cohort was closed as of the cutoff date.

The review division DO2 and OSI selected 2 investigator sites, the study sponsor, and the CRO, (b) (4) for clinical inspection. Dr. Jose Manuel Trigo (Site ES022) had the highest enrollment and a relatively higher number of treatment responders. Dr. Sant Chawla (Site US013) was chosen because it was one of the highest ranked domestic sites. The CRO (b) (4) the contractor for clinical trial monitoring and management of this study, and the study sponsor were also chosen for clinical inspection given this new molecular entity application.

III. RESULTS:

1. Dr. Jose Manuel Trigo, Clinical Investigator (CI) Site ES022
Teatinos, s/n
Malaga, 29010
Spain

This CI was inspected between March 9-12, 2020 as a data audit for the study PM1183-B-005-14. This was the first FDA inspection for this investigator. The site screened 31 subjects and enrolled 21 of them, with 14 in the SCLC cohort. The first subject (Subject (b) (6)) was screened on October 22, 2015 and dosed on November 3, 2015. As of the data cutoff date, 10 of the enrolled subjects remained on study treatment, 11 were discontinued from study treatment due to disease progression, adverse event, or investigator's decision.

Source records for all 14 subjects in the SCLC cohort were reviewed during the inspection. The reviewed records included, but were not limited to, the informed consent forms (ICF), eligibility criteria, laboratory tests, adverse events (AEs), concomitant medications, and electronic case report forms (eCRFs). Regulatory documents related to the conduct and oversight of the study were also reviewed, including the Institutional Ethics Committee approvals of the protocol/amendments, informed consent and associated communications, protocol deviations, management of data entered into eCRFs, study drug accountability, retention of study records, and monitoring visits and communications with the sponsor.

The inspection demonstrated that all 14 subjects in the SCLC cohort met the eligibility criteria and were consented before study treatment initiation. The tumor assessment scans for the primary efficacy endpoint were performed as scheduled and the raw data were submitted electronically to the sponsor via eCRF. The response data were verifiable with source records. There was no underreporting of adverse events or protocol violations identified.

2. (b) (4)

(b) (4) was inspected between (b) (4) for its site monitoring and management of Study PM1183-B-005-14. This CRO has been inspected nine times previously, with NAI as the final compliance classification for each inspection. The most recent inspection was conducted in (b) (4)

For the study PM01183-B-005-14, this CRO was responsible for site monitoring, collection of site regulatory documents, and preparation and submission of application for ethics committee approvals in Italy, Switzerland, and Sweden. The CRO obtained this responsibility after its acquisition of (b) (4)

The inspection included a review of the Contract Agreements, monitoring plans, monitoring visit reports, Standard Operating Procedures (SOPs), training records, and Form 1572s and

Financial Disclosure Forms. The inspector also examined the entire monitoring program, including the monitors' credentials (training and curriculum), monitoring plans for all sites, and monitoring visit reports for the following 6 sites: ES022 (Dr. Trigo's site), US013 (Dr. Chawla's site), US012, ES001, ES012, and GB003.

The inspection revealed that the CRO had adequate monitoring of the study PM01183-B-005-14. The monitoring visits were conducted according to the monitoring plans. All reviewed queries were resolved in a timely manner and all collected documents were submitted to the study sponsor. There was no study site that was terminated early due to non-compliance with the protocol. There were no deficiencies identified in this inspection.

3. Sant Chawla, Clinical Investigator Site US013
2811 Wilshire Blvd
Santa Monica, CA 90403

This clinical investigator was scheduled to be inspected by the Office of Regulatory Affairs (ORA), but was canceled due to the COVID-19 pandemic that has significantly limited OSI's ability to conduct onsite Good Clinical Practice (GCP) inspections. The clinical investigator site was contacted for inspection on March 23, 2020, and the investigator's response showed that the site was unable to accommodate the inspection as the hospital of this site did not allow non-essential personnel to enter due to COVID-19. In addition, there was no possibility of access to records from a remote location. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for this clinical investigator inspection was reevaluated. Following discussions between OSI and DO2, a decision was made by DO2 not to proceed with the planned inspection.

4. Pharma Mar Inc.
Avda. de los Reyes, 1
28770 Colmenar Viejo.
Madrid, Spain

This Sponsor inspection was scheduled on March 16-20, 2020, by the FDA ORA, but was canceled due to the COVID-19 pandemic that has significantly limited OSI's ability to conduct onsite Good Clinical Practice (GCP) inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for this Sponsor inspection was reevaluated. Following discussions between OSI and DO2, a decision was made by DO2 not to proceed with inspection of the Sponsor.

{See appended electronic signature page}

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

CONCURRENCE

{See appended electronic signature page}

Yang-Min (Max) Ning, M.D., Ph.D.
Acting Team Leader
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CC:

Central Doc. Rm. NDA 213702
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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MICHELE B FEDOWITZ
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YANGMIN NING
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KASSA AYALEW
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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 4, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Kwadwo Korsah, RPM
DO2

Subject: QT Consult to NDA 213702 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/14/2020 regarding the sponsor's QT-related submission. We reviewed the following materials:

- Previous IRT review for IND 127944 dated 08/22/2019 in DARRTS;
- Proposed Labeling (Submission 0001);
- Summary of clinical pharmacology and nonclinical safety (Submission 0001).

1 IRT's Evaluation / Internal Comments to the Division

Previously the IRT reviewed a QT assessment report of lurbinectedin based on study PM1183-B-005-14-QT (IND 127944, dated 08/22/2019 in DARRTS). Based on the review, we propose the following edits to the label submitted to Submission 0001. Our changes are highlighted (addition, ~~deletion~~); however, we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

(b) (4)

2 BACKGROUND

Lurbinectedin (also known as PM01183, PM1183, or tryptamicidin; MW: 784.8739 g/mol) is a synthetic compound structurally related to ecteinascidin. The hemiaminal moiety of lurbinectedin recognizes and binds to the exocyclic amino group of guanines in the minor groove of DNA and prevents the binding of oncogenic transcription factors to their recognition sequences and, thus, inhibiting oncogenic transcription. The sponsor is seeking accelerated approval for ZEPSYRE (lurbinectedin) for the treatment of patients with small cell lung cancer (b) (4). The proposed dosing regimen is 3.2 mg/m^2 every 21 days (Q3W) as an intravenous (IV) infusion over 60 minutes.

We previously reviewed a QT assessment report of lurbinectedin based on study PM1183-B-005-14-QT (IND 127944, dated 08/22/2019 in DARRTS). The highest dose that was evaluated was 3.2 mg/m^2 as an 1-hr IV infusion Q3W, which is the proposed therapeutic dose. The data were analyzed using central tendency as the primary analysis, which did not suggest that lurbinectedin is associated with large mean increases in the QTc interval. The findings of this analysis were further supported by the available nonclinical data, exposure-response analysis, and categorical analysis.

ECG parameter	Treatment	Time	Δ (ms)	90% CI (ms)
QTc	Lurbinectedin 3.2 mg/m^2 Q3W	Cycle 1 Day 1, 1 hr post EOI	1.8	(-1.1, 4.8)
QTc	Lurbinectedin 3.2 mg/m^2 Q3W	Cycle 2 Day 1, 3 hr post EOI	5.1	(0.7, 9.4)

Lurbinectedin treatment is associated with significant increase in heart rate. The maximum effect (mean [90% CI]: 18.3 [15.0, 21.6] bpm) as observed at 3-hr post the end-of-infusion (EOI). However, given the magnitude of the observed ΔQTcF in the study, it is unlikely that the effect of lurbinectedin treatment on the QTc interval would be larger than 20 ms within 4-hours after the start of infusion.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

NAN ZHENG
03/04/2020 11:36:10 AM

CHRISTINE E GARNETT
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