CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213702Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213702

Assessment #1

Drug Product Name	Zepzelca (lurbinectedin)
Dosage Form	Lyophilized powder for injection
Strength	4 mg/vial
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Pharma Mar USA, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	12/16/2019	All CMC
Quality Amendment	12/20/2019	DP, OPMA
Quality Amendment	01/15/2020	OPMA
Labeling Amendment	01/27/2020	DP
Quality Amendment	02/14/2020	Microbiology
Quality Amendment	02/25/2020	DS, OPMA
Quality Amendment	03/11/2020	OPMA
Labeling Amendment	03/27/2020	DP
Quality Amendment	04/03/2020	OPMA
Quality Amendment	04/17/2020	Microbiology
Quality Amendment	05/05/2020	OPMA
Quality Amendment	05/14/2020	OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rajan Pragani	Ali Al Hakim
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Manufacturing	Kshitij Patkar	David Anderson
Microbiology	Eric Adeeku	Paul Dexter
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xing Wang	
Laboratory (OTR)	N/A	N/A
Environmental	James Laurenson	N/A

Xing Wang

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete CMC information has been submitted to NDA 213702 and found to be adequate upon completion of the review. All facilities are approvable based on acceptable compliance history. (b) (4)

OPQ recommends **APPROVAL** of NDA 213702 for Zepzelca (lurbinectedin) 4 mg for injection. OPQ grants a 48-month expiration period when stored refrigerated at 2ºC- 8ºC (36ºF- 46ºF). In addition, OPQ grants a (b) (4) re-test period for lurbinectedin drug substance.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Lurbinectedin binds to the minor groove of DNA and is a selective inhibitor of oncogenic transcription. Lurbinectedin is indicated for the treatment of (b) (4)

Lurbinectedin is manufactured (b) (4) Lurbinectedin is insoluble or practically insoluble in water but solubility increases at acidic pH.

Lurbinectedin 4 mg for injection is a sterile, preservative-free, white to off white, lyophilized powder in a 30-mL, single-dose, (b) (4) clear-glass vial. The formulation contains sucrose, lactic acid and sodium hydroxide. Before use, the powder is reconstituted with 8 mL of Water for Injection USP (WFI) to give a solution containing lurbinectedin 0.5 mg/mL (the actual calculated concentration is 0.47 mg/mL based on the final volume of 8.5 mL). The reconstituted solution is diluted further in 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP for intravenous infusion covering the concentration range of lurbinectedin (b) (4) µg/mL. The primary packaging system USP (b) (4) clear-glass vial is closed with (b) (4) rubber stopper and aluminum flip-off seal.

The reconstituted drug product solution was stored in the vials at room temperature with ambient light exposure or under refrigerated (5 ºC ± 3 ºC) conditions for up to 24 hours. Physicochemical and microbiological in-use stability of the diluted drug product solution in either 0.9 % Sodium Chloride Injection USP or 5 % Dextrose Injection USP for intravenous infusion has been demonstrated for up to 24 hours at either room temperature with ambient light exposure or under refrigerated (5ºC ± 3 ºC) conditions. Protection from light is not necessary for the drug product, according to the results of the photostability studies under ICH conditions.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with SCLC (b) (4) .
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	5.184 mg (based on 1.62 m^2 BSA)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance lurbinectedin is (b) (4) Lurbinectedin possesses a total of 7 stereogenic centers with the following configuration: *6R, 6aR, 7R, 13S, 14S, 16R, 20/1'R*. One of the regulatory starting materials (b) (4) . The NDA submission references DMF (b) (4) for the full drug substance information. The DMF was reviewed and deemed adequate. Two specified impurities (impurity (b) (4)) have specification limits above the ICH Q3A qualification threshold. The nonclinical reviewer concluded that both limits are adequately qualified. As a part of the overall control strategy, the drug substance specification is adequate. The batch data provided demonstrates manufacture of drug substance with acceptable quality. Based on the stability data provided for the registration batches in the DMF, a proposed retest date of (b) (4) is acceptable for lurbinectedin.

Drug Product: Adequate

Lurbinectedin 4 mg for injection is a sterile, preservative-free, white to off white, lyophilized powder in a 30-mL, single-dose, (b) (4) clear-glass vial. Before use, the powder is reconstituted with 8 mL of Water for Injection USP (WFI) to give a solution containing lurbinectedin 0.5 mg/mL. The reconstituted solution is diluted further in 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP for intravenous infusion covering the concentration range of lurbinectedin (b) (4) µg/mL. The primary packaging system USP (b) (4) clear-glass vial is closed (b) (4) rubber stopper and aluminum flip-off seal. The formulation contains sucrose, lactic acid and sodium hydroxide.
Quality control specification (same for release and stability) appears to be reasonable. Drug product testing is conducted by following ICH Q6A, ICH Q3B, ICH Q3D, and USP <1151>, <1>, <232> monographs and is deemed adequate. A detailed risk assessment accordance with the ICH Q3D / USP <232> is provided for elemental impurities. The HPLC method has been validated for accuracy, precision, specificity, and linearity per ICH Q2 recommendations, and is stability indicating.

During the pharmaceutical development, the extractable volume, dose recovery, and concentration of the reconstituted drug product solution was determined for six batches of lurbinectedin 4 mg in a 30-mL clear glass vial. The lurbinectedin dose recovery was ≥ 95% with respect to the nominal dose for all batches of lurbinectedin 4 mg in a 30-mL clear glass vial.
The reconstituted drug product solution was stored in the vials at room temperature with ambient light exposure or under refrigerated (5 ºC ± 3 ºC) conditions for up to 24 hours. Physicochemical and microbiological in-use stability of the diluted drug product solution in either 0.9 % Sodium Chloride Injection USP or 5 % Dextrose Injection USP for intravenous infusion has been demonstrated for up to 24 hours at either room temperature with ambient light exposure or under refrigerated (5ºC ± 3 ºC) conditions. Protection from light is not necessary for the drug product, according to the results of the photostability studies under ICH conditions.
The proposed expiration dating period of 48 months for lurbinectedin 4 mg when stored refrigerated at 2ºC- 8ºC (36ºF- 46ºF) in the proposed primary container closure system may be Granted.

Labeling: Adequate

All CMC comments/edits have been conveyed to OND and the applicant.

Note: The product is a 4 mg/vial lyophilized powder for injection. The powder is reconstituted with 8 mL WFI with the total volume being approx. 8.5 mL. Although, the intent may have been to get the 0.5 mg/ml reconstituted solution (4 mg/8 mL), the actual concentration that will be achieved based on the 4 mg in the vial and 8.5 mL total solution volume will be 0.47 mg/mL. A note was added in Section 11 of the USPI to explain the actual concentration after reconstitution. The applicant used a rounding up of actual concentration of 0.47 mg/mL to 0.5 mg/mL for the label throughout the clinical development. The applicant justified the label claim concentration (0.5 mg/mL with one decimal place rather than 0.47 mg/mL) based on FDA Guidance, 'Safety Considerations for Product Design to Minimize Medication Errors, April 2016'. The formula to calculate the required volume of reconstituted solution in Section 2.4 of the USPI remains using 0.5 mg/mL. This will keep the recommended dose and dose reduction consistent with what have been used in clinical trials.

Manufacturing: Adequate

The proposed drug product Lurbinectedin 4 mg for injection is manufactured by

(b) (4)

for the concentration has yet to be finalized by ORP/OPPQ. Therefore, no further action is indicated at this time.
The applicant initially proposed two manufacturing sites for the commercial production of the drug product. (b) (4) The lyophilization operation is validated. The exhibit batches and proposed commercial scale batches are same and no scale-up of primary batches for commercial product is proposed. (b) (4) No reprocessing is proposed.

Microbiology: Adequate

The sponsor was contacted via the Agency's 01/16/2020 IR to address minor deficiencies that were identified during filing review. The information provided in the IR response submissions dated 02/14/2020, 03/11/2020 and 04/17/2020 were reviewed and were found adequate. Overall manufacturing operations are found adequate from a microbiology perspective --- refer to microbiology review for detail. Microbiological tests in the product release specification are adequate. Adequate container-closure integrity (b) (4) was demonstrated. The USP <51> acceptance criterion was met and the storage time of 24 h is affirmed for the reconstitution and dilution agents at the proposed storage temperatures.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability At release and stability)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Osmolality	Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development	Acceptable	Controls are in place (refer to the Pharmaceutical Development section)
Deliverable volume	Formulation • Container closure • Process parameters • Scale/equipments • Site	L	Assessed during Development	Acceptable	Justification is provided Controls are in place
Sterility	Formulation • Container closure • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Justification is provided, refer to OPF review.
Endotoxin	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Justification is provided, refer to OPF review.
pH	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place
Particulate matter (non aggregate for solution only) **(Reconstitution And diluted solution)**	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	USP <381., <660> tests conform

Application Technical Lead Name and Date:

Xing Wang, Ph.D.

Xing Wang

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U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	04/13/2020	Refer to DS review
	III			Adequate	04/22/2020	DMFs not reviewed per MAPP 5015.5 (Rev. 1).
	III			Adequate		
	V			Adequate		
	V			Adequate		

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	(b) (4)	Drug development
IND	127944	Drug development

2. CONSULTS None

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LABELING

R Regional Information

1.14 Labeling

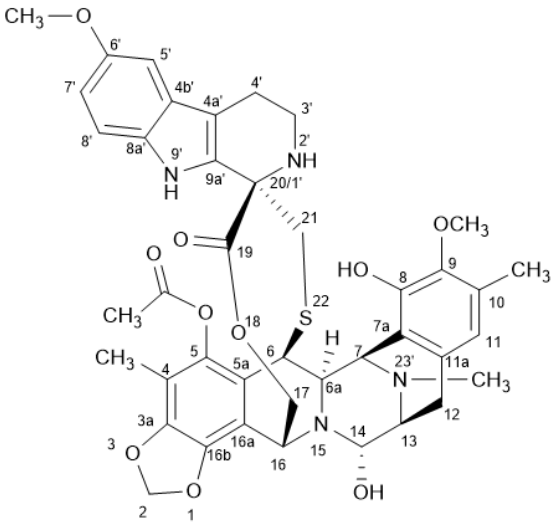
Labeling & Package Insert

DESCRIPTION section:

11 DESCRIPTION

ZEPSYRE is an alkylating drug. The chemical name of TRADENAME (lurbinectedin) is (1'R,6R,6aR,7R,13S,14S,16R)-8,14-dihydroxy-6',9-dimethoxy-4,10,23-trimethyl-19-oxo-2',3',4',6,7,9',12,13,14,16-decahydro-6aH-spiro[7,13-azano-6,16-(epithiopropanooxymethano) [1,3]dioxolo[7,8]isoquinolino[3,2-b][3]benzazocine-20,1'-pyrido[3,4-b]indol]-5-yl acetate.

The molecular formula is $C_{41}H_{44}N_4O_{10}S$. The molecular weight is 784.87g/mol, and the chemical structure is:



TRADENAME 4 mg is supplied as a lyophilized powder in a single-dose vial for reconstitution. The TRADENAME lyophilized formulation is comprised of 4.0 mg lurbinectedin (b) (4), sucrose (800 mg), lactic acid (22.1 mg), and sodium hydroxide (5.1 mg). Before use, the lyophilizate is reconstituted by addition of 8 mL Sterile Water for Injection USP, yielding a solution containing 0.5 mg/mL lurbinectedin.

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TRADENAME (lurbinectedin) for injection is supplied as a sterile, preservative-free, white to off-white lyophilized powder in a (b) (4) single-dose clear glass vial. Each carton (NDC (b) (4) contains one single-dose vial.

Storage and Handling

Store refrigerated at 2° to 8°C (36° to 46°F)

ZEPSYRE is a (b) (4) drug. Follow applicable special handling and disposal procedures[1].

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of TRADENAME is 3.2 mg/m^2 by intravenous infusion over 60 minutes every 21 days until disease progression or unacceptable toxicity.

Initiate treatment with TRADENAME only if absolute neutrophil count (ANC) is at least 1,500 cells/mm^3 and platelet count is at least 100,000/mm^3.

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?
☒ Yes ☐ No ☐ N/A

If "No," explain.

R Regional Information

1.14 Labeling

Commercial packaging:

Immediate vial Container Label:

(b) (4)

Secondary carton:

(b) (4)

Reviewer's Assessment: *The deficiencies were identified (change* (b) (4) *to "For injection" and* (b) (4) *to single-dose on primary vial label) will be communicated to the applicant by DMEPA. A final version of the agreed upon PI will be reviewed by the ATL and included in their memo.*

Reviewer's Assessment:

The labeling of the PI and container labels is revised per labeling tools to have the most current information of the labels.

Conclusion: *Labels and Labeling are adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 10-APR-2020

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, PhD, April 13, 2020

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	213702
Assessment Cycle Number	01
Drug Product Name/ Strength	Lurbinectedin / 4 mg/vial
Route of Administration	Intravenous infusion
Applicant Name	Pharma Mar USA, Inc.
Therapeutic Classification/ OND Division	Type 1 – New Molecular Entity
Manufacturing Sites	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary: The submission is **recommended** for approval.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
1	12/16/2019
9	02/14/2020
14	03/11/2020
21	04/17/2020

List Submissions being assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
12/16/2019	12/16/2019	N/A	01/03/2020
02/14/2020	02/14/2020	N/A	02/14/2020
03/11/2020	03/11/2020	N/A	03/26/2020
04/17/2020	04/17/2020	N/A	04/17/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks:

This is an electronic submission.
Goal date is 08/16/2020.
The NDA has orphan drug designation.

The sponsor was contacted via the Agency's 01/16/2020 IR to address minor deficiencies that were identified during filing review. The information provided in the IR response submissions dated 02/14/2020, 03/11/2020 and 04/17/2020 were reviewed and incorporated in this review. The most recent deficiencies wherever necessary are directly reproduced in italic with a response provided.

Concise Description of Outstanding Issues

No outstanding issues remain.

Supporting Documents:

DMF (b) (4) (Type V): – (b) (4) (b) (4)

(b) (4) mic3.doc – Sterility assurance review of the (b) (4) (b) (4) that was found adequate on 11/10/2005.

(b) (4) .doc – Sterility assurance review of the (b) (4) that was found adequate on 02/03/2017.

DMF (b) (4) (Type V): – (b) (4)

(b) (4) .docx – Sterility assurance review of the (b) (4) that was found adequate on 08/14/2019.

(b) (4) .docx – Sterility assurance review of one of the drug product manufacturer's sterile products that used the same (b) (4) reviewed and found adequate in the 12/10/2018 microbiology review.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product –
(section 3.2.P.1).

Lurbinectedin 4 mg for injection is presented as a sterile, preservative-free, white to off white, lyophilized powder in a 30-mL/20 mm, single-dose, (b) (4) clear-glass vial. Before use, the powder is reconstituted with 8 mL of Water for Injection USP (WFI) to give a solution containing lurbinectedin 0.5 mg/mL.

Drug product composition –
(section 3.2.P.1).

Ingredient	Content (mg/vial)
Lurbinectedin	4.0 mg
Sucrose, NF	800 mg
Lactic acid, USP	22.08 mg

Sodium hydroxide, NF	5.12 mg
Water for Injection, USP	8.0 mL

Description of container closure system –

(b) (4)

The applicant provided adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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(b) (4)

Adequate

Antimicrobial Effectiveness Testing

N/A. The subject drug product is single dose; therefore, antimicrobial effectiveness testing is not required.

P.3 MANUFACTURE

(b) (4)

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Eric Adeeku

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