CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213702Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	213702
PDUFA Goal Date	August 16, 2020
OSE RCM #	2019-2598
Reviewer Name	Victoria Sammarco, Pharm.D., MBA
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 8, 2020
Subject	Evaluation of Need for a REMS
Established Name	lurbinectedin
Trade Name	Zepzelca
Name of Applicant	Pharma Mar USA, Inc.
Therapeutic Class	Alkylating drug
Formulation(s)	4 mg lyophilized powder for injection in single-dose vial
Dosing Regimen	3.2 mg/m^2 intravenously over 1 hour every 3 weeks

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Zepzelca (lurbinectedin) is necessary to ensure the benefits outweigh its risks. Pharma Mar USA, Inc. submitted a New Drug Application (NDA) 213702 for lurbinectedin with the proposed indication of [redacted] (b) (4). The risks associated with lurbinectedin include myelosuppression, [redacted] (b) (4) and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) and Oncology Center of Excellence (OCE)/Office of Oncologic Diseases (OOD) agree that a REMS is not needed to ensure the benefits of lurbinectedin outweigh its risks. The efficacy of lurbinectedin was supported by Study B-005's small cell lung cancer (SCLC) cohort, in which the lurbinectedin group had a confirmed overall response rate of 35% (95% CI: 26, 45). The serious risks associated with lurbinectedin of myelosuppression, [redacted] (b) (4) and embryo-fetal toxicity will be addressed in the warnings and precautions section of the label. The likely prescribers will be hematologists and oncologists who have experience managing the serious adverse events reported with lurbinectedin. Based on the benefit: risk profile with consideration of the severity of the disease, expertise of prescribers and the expected benefit over current therapies, the DRM and OCE/OOD recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Zepzelca (lurbinectedin) is necessary to ensure the benefits outweigh its risks. Pharma Mar USA, Inc. submitted New Drug Application (NDA) 213702 for lurbinectedin with the proposed indication of [redacted] (b) (4) This application is under review in the Division of Oncology Products 2 (DOP2). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Lurbinectedin, a new molecular entity[a], is part of the established pharmacological class (EPC) of alkylating drugs and is indicated for the treatment of metastatic small cell lung cancer in adult patients [redacted] (b) (4).[1] The mechanism of action of lurbinectedin partially resides with the drug's ability to covalently bind to the exocyclic amino group of guanines in the minor groove of GC rich DNA sequences. Binding causes the bending of DNA which ultimately results in double strand breaks, and subsequent cell death. The Applicant presented additional data showing an association between lurbinectedin and degradation of phosphorylated RNA polymerase II, leading to decreased transcription.[2] Lurbinectedin's proposed dosing regimen is 3.2 mg/m^2/dose as a 1-hour intravenous infusion given every three weeks until disease progression or

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

unacceptable toxicity.[b] The infusion will likely occur in inpatient and outpatient centers capable of providing infusions and infusion-related support. Currently, lurbinectedin is not approved in any jurisdiction.

Lurbinectedin was designated as fast track designation and orphan drug designation. If approved, the indication will be approved under accelerated approval based on overall survival (OS) and duration of response (DOR).

2.2 RELEVANT REGULATORY HISTORY

- 11/21/2008 - Pre-IND meeting held to discuss the development strategy of PM01183 (lurbinectedin) for the treatment of solid tumors.
- 10/09/2015 - IND 127944 submitted to DOP2 with new clinical protocol, Protocol PM1183-C-003-14, entitled "Phase 3 Randomized Clinical Trial of Lurbinectedin (PM01183) plus Doxorubicin (DOX) versus Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS Trial)."
- 11/03/2015 - FDA placed IND 127944 on full clinical hold due to the concern that the protocol design does not allow for isolation of the relative contribution of PM01183 (lurbinectedin) when used in combination with doxorubicin and the study would not be able to meet its stated objectives.
- 01/28/2016 - A Type A meeting was held to further discuss the design of the ATLANTIS trial and Pharma Mar's proposal to address the clinical hold placed on IND 127944. FDA recommended an adaptive study design with single-agent doxorubicin and single-agent lurbinectedin arms with the opportunity to drop arms for futility at interim analysis, to allow isolation of the contribution of each drug to the regimen.
- 03/11/2016 - Clinical hold on IND 127944 was removed after a revised clinical protocol and statistical analysis plan for the ATLANTIS study was submitted.
- 08/01/2018 - Lurbinectedin received orphan designation for the treatment of small cell lung cancer.
- 12/11/2018 - A Type B, End of Phase 2 meeting was held to discuss results from the SCLC cohort of Study B-005. Pharma Mar stated intent to use data from Study B-005 to support an application for accelerated approval of lurbinectedin for the treatment of patients with (b) (4) SCLC with disease progression on or after (b) (4) chemotherapy and for the ongoing ATLANTIS trial to serve as the confirmatory study to verify clinical benefit.
- 12/16/2019 - NDA 213702 submission for lurbinectedin received.
- 02/13/2020 - Fast track designation granted.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 03/05/2020 - A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for lurbinectedin.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Lung cancers of all types accounted for 150,000 deaths in 2016 making it the deadliest of all cancer types.[3] Small cell lung cancer (SCLC) accounts for 13-15% of all lung cancers with smoking being the primary risk factor.[c,4] SCLC is generally highly responsive to chemotherapy and radiotherapy but usually recurs within 14-15 months for patients with limited-stage disease and 5-6 months for patients with extensive-stage disease. The median survival of patients with relapsed SCLC is usually 2-6 months.[5]

3.2 Description of Current Treatment Options

The second line treatment in patients with recurrent or refractory disease is dictated by the patient's initial treatment and time to disease recurrence. If relapse occurs beyond six months of preliminary treatment, the initial chemotherapy regimen should be repeated (usually platinum-based +/- immunotherapy).[4] If relapse occurs within six months, topotecan (oral or intravenous) or a clinical trial is recommended.[6] Topotecan is currently the only FDA-approved agent with the indication of treatment of small cell lung cancers in patients with chemotherapy-sensitive disease after failure of first-line chemotherapy. Chemotherapy sensitivity is defined as disease progression at least 60 days after initial chemotherapy per intravenous topotecan labeling[7] (45 days from end of initial chemotherapy for oral topotecan[8]). Other recommended regimens for refractory relapsed or resistant disease if topotecan or a clinical trial is not an option include:[5]

- nivolumab +/- ipilimumab
- pembrolizumab
- paclitaxel
- irinotecan
- temozolomide
- cyclophosphamide/doxorubicin/vincristine (CAV)
- oral etoposide
- vinorelbine
- gemcitabine
- bendamustine

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Immunotherapy is generally preferred if the patient did not receive it in their initial therapy. Radiation therapy may be used in conjunction with systemic chemotherapy both for treatment and symptom palliation.[5]

Subsequent treatment of any kind in SCLC carries a median survival of only 4-5 months. Though single agent topotecan compared favorably to other proposed treatments, the overall survival rate at one year for patients with sensitive relapse (relapse beyond 60-90 days from treatment) is 27%. When used in refractory relapsed or resistant disease (relapse within 60-90 days from treatment), the one-year survival rate is 9%. [9] An unmet need exists for efficacious treatment of recurrent disease, especially in those with refractory relapsed and resistant disease.

The safety of agents used to treat relapsed SCLC must be viewed in light of the mortality of the disease. Topotecan carries a boxed warning against administration in patients who have active bone marrow suppression (ANC < 1,500 cells/mm^3). Bone marrow suppression occurred in 50-75% of clinical trial participants and is considered the dose limiting toxicity of topotecan. Additionally, topotecan's warnings and precautions include risk of neutropenic colitis, interstitial lung disease, and embryofetal toxicity. [6]

4 Benefit Assessment

The pivotal trial NCT 02454972 (study B-005) supporting this application consists of an ongoing phase 2 basket (non-comparative) clinical trial evaluating the efficacy and safety of lurbinectedin at 3.2 mg/m2 q3wk in 335 treated patients with nine difficult-to-treat tumor types with disease progression after available therapy, including 105 patients with SCLC. The study was conducted in 38 centers throughout the US and Europe. Study B-005's primary endpoint was investigator-assessed overall response rate (ORR) and secondary endpoints included median duration of response (DoR), progression free survival and overall survival. Primary investigators measured an ORR of 35% (95% CI: 26, 45) in the SCLC cohort.[d] Good activity was observed in the sensitive population (chemotherapy free treatment interval (CFTI) ≥ 90 days; ORR=43.3% and DoR=5.3 months by independent review committee (IRC)) and activity was notable in the resistant population (ORR=13% and DoR=4.8 months by IRC). These conclusions were evaluated in the concert with lurbinectedin's favorable safety profile, particularly with respect to myelosuppression and related complications as compared to topotecan. The clinical reviewer concluded that the Sponsor provided substantial evidence of effectiveness to meet the requirements for accelerated approval of lurbinectedin for the treatment of adult patients with (b) (4) SCLC (b) (4) Continued approval for this indication will be contingent upon verification and description of clinical benefit in the ATLANTIS phase 3 trial.

5 Risk Assessment & Safe-Use Conditions

The safety of lurbinectedin was primarily evaluated through an integrated safety data set (ISA) from studies B-005 (including the SCLC cohort), a multi-cohort basket trial, and C-004, a trial in platinum-

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

resistant ovarian cancer. These two trials together enrolled 554 patients. Further supporting data were taken from a pooled cohort of various doses and schedules of single agent lurbinectedin in 801 patients.[10] Serious adverse reactions[e] that were considered related to therapy occurred in 88/554 (16%) patients in the ISA group. These serious adverse reactions included myelosuppression (most common), febrile neutropenia, GI-related events, and/or physical health deterioration. Adverse reactions leading to drug discontinuation occurred in 31/554 (6%) while dose reduction was alternatively used in 100/554 (18%). There were also 35/554 (6.3%) treatment-emergent deaths that were largely attributed to disease progression though 4 deaths were attributed to an infectious etiology in a compromised host.[9, f]

Adverse events occurring in >20% of the SCLC cohort included fatigue, GI disorders, dyspnea, and neutropenia. Serious risks requiring targeted risk messaging include bone marrow suppression, (b) (4) , and embryo-fetal toxicity.

5.1 MYELOSUPPRESSION

Reversible myelosuppression was the most common adverse event seen in the ISA and SCLC subpopulation. Grade 3 neutropenia occurred in 40.6% and 45.7% in the ISA and B-005 SCLC subpopulation respectively and grade 4 neutropenia occurred in 21.7% and 24.8%. Neutropenia generally occurred around day 15 post infusion and resolved after a median of 6-7 days.[9] Grade 3/4 thrombocytopenia was also observed in both the ISA population and the B-005 SCLC subpopulation at 9.9% and 6.7% respectively for grade 3, and 4.5% and 3.8% for grade 4. Thrombocytopenia generally occurred on day 10 post infusion, lasted 5.5-7.5 days on average and was not associated with major bleeding events in clinical trials.[9] The sponsor recommends adequate bone marrow reserves before treatment is commenced as evidenced by neutrophil counts of at least 1,500 cells/mm^3 and platelet counts greater than or equal to 100,000/mm^3. The sponsor advises that the dose should be reduced from 3.2 mg/m^2 to 2.6 mg/m^2 for the first incidence and to 2.0 mg/m^2 for a recurrence in the following treatment-related clinical scenarios:

- grade 4 thrombocytopenia
- grade 3 thrombocytopenia with bleeding requiring transfusion
- grade 4 neutropenia
- any grade neutropenia associated with infection
- any adverse reaction that requires frequent or prolonged (>2 weeks) dose delays

[e] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Treatment should be discontinued at the third incidence of the listed hematologic toxicity scenarios. Secondary prophylaxis with G-CSF is recommended in grade 4 neutropenia and any grade neutropenia associated with infection. If approved, this risk will be communicated in the warnings and precautions and dose modifications for adverse reactions section of the label.[11]

5.2 (b) (4)

Transaminase increases from baseline were common in the ISA and SCLC cohort. Sixty to seventy percent of patients studied experienced increases in ALTs and approximately 40% experienced increases in ASTs. Severe elevations in ALTs and ASTs occurred in less than 10% of subjects. Bilirubin was also elevated from baseline in approximately 10% of patients.[9] Transaminase increases alone or with other adverse events caused a total of five dose reductions in the ISA population, and one dose reduction in the B-005 SCLC subpopulation. No Hy's Law cases were observed. Proposed labeling includes that regular monitoring of liver tests should occur (b) (4) If approved, this risk will be communicated in the warnings and precautions and dose modifications for hepatic impairment section of the label. [10] The Applicant is also asked to submit a post-marketing requirement (PMR) of a final report (including analysis and datasets) 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. Final report submission is scheduled for September 2025.

5.3 Embryo-Fetal Toxicity

Lurbinectedin can cause fetal harm based on animal studies. Studies in pregnant rats administered a single dose of 0.6 mg/m2 of lurbinectedin during the period of organogenesis showed 100% embryo-fetal lethality as well as maternal toxicity.[9] No clinical data is available with lurbinectedin in pregnancy in humans. The proposed label recommends that females of reproductive potential should use effective contraception during treatment and for 6 (b) (4) after the last dose and males with female partners of reproductive potential should use effective contraception during treatment and for (b) (4) months after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

6 Expected Postmarket Use

If approved, lurbinectedin will primarily be used in both inpatient and outpatient settings. The likely prescribers will be hematologists and oncologists, who are aware of the risks and can appropriately manage patients requiring cytotoxic chemotherapy.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for lurbinectedin beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The OCE/OOD recommends approval of lurbinectedin based on the efficacy and safety information currently available. The indication will be approved under accelerated approval based on ORR. Lurbinectedin is an alkylating drug (b) (4)

The efficacy of lurbinectedin is supported by Study B-005 in which an ORR of 35% was established. The serious risks associated with lurbinectedin include myelosuppression, (b) (4) and embryo-fetal toxicity and will be communicated in labeling.

SCLC accounts for 13-15% of all lung cancers and is the cause of more than 20,000 deaths per year in the US.[4] Though generally highly responsive to chemotherapy and radiotherapy, SCLC usually recurs within 14-15 months for patients with limited-stage disease and 5-6 months for patients with extensive-stage disease and the median survival of patients with relapsed SCLC is usually 2-6 months despite current treatment options.[5] Lurbinectedin will be used by hematologists and oncologists for SCLC who are adept at managing the adverse effects of cytotoxic chemotherapeutic agents such as lurbinectedin. Based on the benefit: risk profile of lurbinectedin with special consideration of the severity of the disease, expertise of prescribers and the expected benefit over current therapies, the DRM and OCE/OOD recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable. Risks are adequately conveyed and the healthcare providers who will be administering lurbinectedin routinely manage identified risks. Therefore, a REMS is not necessary for lurbinectedin to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety and efficacy information collection per the ATLANTIS phase 3 trial and labeling negotiations are ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Pharma Mar USA, Inc. Lurbinectedin. Module 2.5. Clinical Overview. December 16, 2019.

[2] NDA 213702 Lurbinectedin (Zepzelca) Unireview, Date June 2, 2020.

[3] (2020). USCS Data Visualizations. [online] Available at: https://gis.cdc.gov/Cancer/USCS/DataViz.html [Accessed 3 Mar. 2020].

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[6] Small Cell Lung Cancer. (2019). NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network.

[7] Topotecan injection package insert. Sellersville, PA: Teva Pharmaceuticals USA; 2014 February.

[8] Hycamtin (topotecan) capsules package insert. Research Triangle Park, NC: GlaxoSmithKline; 2007.

[9] Horita, N., Yamamoto, M., Sato, T., Tsukahara, T., Nagakura, H., Tashiro, K., Shibata, Y., Watanabe, H., Nagai, K., Inoue, M., Nakashima, K., Ushio, R., Shinkai, M., Kudo, M. and Kaneko, T. (2015). Topotecan for Relapsed Small-cell Lung Cancer: Systematic Review and Meta-Analysis of 1347 Patients. Scientific Reports, 5(1).

[10] Pharma Mar USA, Inc. Lurbinectedin. Module 2.7.4. Summary of Clinical Safety. December 16, 2019.

[11] Proposed prescribing information for lurbinectedin as currently edited by FDA, Accessed May 18, 2020.

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/s/

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