CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214383Orig1s000

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	214383
PDUFA Goal Date	February 28, 2021
OSE RCM #	2020-1375
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	February 11, 2021
Subject	Evaluation of Need for a REMS
Established Name	Melphalan flufenamide
Trade Name	Pepaxto
Name of Applicant	Oncopeptides AB
Therapeutic Class	Alkylating drug
Formulation(s)	20 mg lyophilized powder
Dosing Regimen	40 mg intravenously on Day 1 of treatment cycle

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) melphalan flufenamide is necessary to ensure the benefits outweigh its risks. Oncopeptides AB submitted a New Drug Application (NDA) 214383 for melphalan flufenamide with the proposed indication for the treatment in combination with dexamethasone, of adult patients with multiple myeloma whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD-38 monoclonal antibody[a].

Melphalan flufenamide has risks of thrombocytopenia, neutropenia, anemia, infections, increased risk of mortality with higher than recommended doses, secondary malignancies, and embryo-fetal toxicity. A boxed warning is not proposed for any risk.

The applicant did not propose a REMS or a risk management program for melphalan flufenamide. DRM agrees that a REMS is not needed to ensure the benefits of melphalan flufenamide outweigh its risks for the proposed indication. The risks of thrombocytopenia, neutropenia, anemia, infections, increased risk of mortality with higher than recommended doses, secondary malignancies, and embryo-fetal toxicity can be adequately described in the labeling. Healthcare providers who will prescribe and administer melphalan flufenamide are expected to be able to manage the melphalan flufenamide-emergent adverse events without additional risk mitigation measures beyond labeling.

1 Introduction

This review by the DRM evaluates whether a REMS for the NME melphalan flufenamide is needed to ensure its benefits outweigh its risks. Oncopeptides AB submitted a New Drug Application (NDA) 214383 for melphalan flufenamide with the proposed indication for the treatment in combination with dexamethasone, of adult patients with multiple myeloma whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD-38 monoclonal antibody.

2 Background

2.1 PRODUCT INFORMATION

[a] The division has changed the indication statement to, "for the treatment of adult patients with refractory multiple myeloma who have received 4 or more lines of therapies and refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. "

Melphalan flufenamide, a new molecular entity[b], is to be supplied as 20 mg lyophilized powder. In Melphalan flufenamide, melphalan is bound to flufenamide, making the drug an NME, and increasing its efficacy. The proposed dose is 40 mg on Day 1 of each 4-week treatment cycle. Treatment continues until disease progression or unacceptable toxicity.[c] Melphalan flufenamide is not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214383 relevant to this review:

- 3/16/2015: Orphan Drug Designation granted for melphalan flufenamide for the treatment of plasma cell myeloma (multiple myeloma).
- 12/3/2019: Pre-NDA meeting; REMS not discussed (DRM did not participate in the meeting)
- 6/30/2020: NDA submitted
- 10/15/2020: Mid-cycle meeting held

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Multiple myeloma is a cancer of differentiated plasma cells. Multiple myeloma occurs mostly in the elderly, with a median age at onset of 69 years. Multiple myeloma is the second most common hematologic malignancy with an estimated 32,110 patients with myeloma diagnosed in the US in 2019. The disease has a 5-year survival of about 52%.[d,1]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment options include drug therapy and stem cell transplantation. Drugs used to treat multiple myeloma include alkylating agents, bortezomib, carfilzomib, daratumumab, doxorubicin, elotuzumab, isatuximab, ixazomib, lenalidomide, panobinostat, pomalidomide, selinexor, and steroids.[2]

4 Benefit Assessment

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

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

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

The efficacy of melphalan flufenamide in combination with dexamethasone was studied in a multicenter, single-arm trial in 157 patients with relapsed refractory multiple myeloma. Patients received melphalan flufenamide 40 mg intravenously on Day 1 and dexamethasone (Days 1, 8, 15 and 22) of each 28-day cycle until disease progression or unacceptable toxicity. The median age of patients was 65 years (range, 35 to 86), 59% were male, 85% were White and 7% were Black or African American. Efficacy was measured by overall response rate and duration of response. The overall response was 25.5% (95% confidence interval, 17.4, 35.1). The duration of response was 5.5 months (3.2, 7.6).

5 Risk Assessment & Safe-Use Conditions

The safety database comprises 157 patients. The most frequently reported adverse events were thrombocytopenia (occurred in 82% of patients in the clinical trial), neutropenia (78%), anemia (71%), infection (58%), and leukopenia (36%). Discontinuation of melphalan flufenamide due to an adverse reaction occurred in 22% of patients. Adverse reactions resulted in dose interruptions in 62% of patients and resulted in dose reductions in 27% of patients.

The safety issues in the draft *Warnings and Precautions* section of the labeling include thrombocytopenia, neutropenia, anemia, infections, increased risk of mortality with higher than recommended doses, secondary malignancies, and embryo-fetal toxicity. A boxed warning has not been proposed for any risk.[e]

5.1 THROMBOCYTOPENIA

Melphalan flufenamide can cause serious thrombocytopenia. Thrombocytopenia of any Grade occurred in 82% of patients, and Grade 3 or 4 thrombocytopenia occurred in 26% of patients. The draft labeling advises healthcare providers to monitor platelets at baseline, during treatment, and as clinically indicated, and to withhold melphalan flufenamide if platelet count is less than (b) (4) x 10^9/L.

5.2 NEUTROPENIA

Melphalan flufenamide can cause serious neutropenia. Neutropenia of any Grade occurred in 78% of patients, and Grade 3 or 4 neutropenia occurred in 34% of patients.
The draft labeling advises healthcare providers to monitor platelets at baseline, during treatment, and as clinically indicated, and to withhold melphalan flufenamide if the absolute neutrophil count is less than 1 x 10^9/L. Patients should be monitored for signs of infection.

5.3 ANEMIA

[e] 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.*

Melphalan flufenamide can cause serious anemia. Anemia of any Grade occurred in 71% of patients, and Grade 3 anemia occurred in 42% of patients, and Grade 4 anemia occurred in 0.6% of patients. The draft labeling advises healthcare providers to monitor red cell counts at baseline, during treatment, and as clinically indicated, and to delay the dose or decrease the dose of melphalan flufenamide if needed to allow recovery of red blood cells.

5.4 INFECTIONS

Infection was reported in 58% of patients who received melphalan flufenamide. Respiratory tract infection occurred in 24% (Grade ≥3, 5%), pneumonia in 13% (Grade ≥3, 11), and sepsis in 1.3% of patients (Grade ≥3, 1.3%). The draft labeling advises healthcare providers to monitor for infection.

5.5 INCREASED RISK OF MORTALITY WITH PEPAXTO AT DOSAGES HIGHER THAN RECOMMENDED DOSAGE

A nonclinical study in dogs showed higher mortality in dogs when melphalan doses exceeded recommended doses. There is limited clinical information using higher than recommended doses.

5.6 SECONDARY INFECTIONS

Secondary malignancies such as myelodysplastic syndromes or acute leukemia have occurred in patients with multiple myeloma who have received melphalan flufenamide. The draft labeling advises healthcare providers to monitor patients long-term after receiving melphalan flufenamide for the development of secondary malignancies.

5.7 EMBRYO-FETAL TOXICITY

Based on the mechanism of action, it is believed that melphalan flufenamide can cause embryo-fetal toxicity. The draft labeling advises that females of reproductive potential should use effective contraceptive during treatment with melphalan flufenamide and for six months after the final dose. Pregnant women should be advised of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during treatment with melphalan flufenamide and for 3 months after the last dose.

6 Expected Postmarket Use

Melphalan flufenamide would likely be used by oncology infusion centers and hospitals.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or other risk mitigation measures.

8 Discussion of Need for a REMS

The clinical team has concluded the data support a favorable benefit:risk assessment for melphalan flufenamide with the proposed indication "for the treatment of adult patients with refractory multiple myeloma who have received 4 or more lines of therapies and refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody." Study data submitted showed an overall response rate of 25.5% (95% confidence interval, 17.4, 35.1). The duration of response was 5.5 months (3.2, 7.6).

The clinical team's preliminary findings are that the application is appropriate for accelerated approval and the risks of thrombocytopenia, neutropenia, anemia, infections, increased risk of mortality with dosages higher than recommended doses, secondary malignancies, and embryo-fetal toxicity will be included in *Warnings and Precautions.* None of the risks warrants a boxed warning.[f] The clinical reviewers believe the adverse events are manageable with dose reduction, interruption, or discontinuance, and the events are appropriately handled with labeling alone.

This reviewer recommends that, should melphalan flufenamide be approved, a REMS is not needed to ensure its benefits outweigh its risks. The risks can be adequately described in the labeling. Melphalan flufenamide will most likely be prescribed by oncologists and used in oncology infusion centers and hospitals. Healthcare providers who will prescribe and administer melphalan flufenamide are expected to be able to manage the melphalan flufenamide-emergent adverse events without additional risk mitigation measures beyond labeling.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of melphalan flufenamide outweigh its risks. At the time of this review, evaluation of safety information and labeling was 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] https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed November 30, 2020.

[f] The clinical review was ongoing at the time of this review.

[2] https://www.cancer.org/cancer/multiple-myeloma/treating/chemotherapy.html. Accessed November 30, 2020.

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