# NEW DRUG APPROVAL

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| **Brand Name** | Pepaxto® |
| **Generic Name** | melphalan flufenamide; melflufen |
| **Drug Manufacturer** | Oncopeptides, Inc. |

## New Drug Approval

FDA Approval Date: February 26, 2021

Review Designation: Priority; Orphan

Type of Review: Type 1 - New Molecular Entity, New Drug Application (NDA): 214383

Dispensing Restriction: Specialty, Limited Distribution

## Place in Therapy

### DISEASE DESCRIPTION & EPIDEMIOLOGY

Multiple myeloma (MM) is an incurable cancer of the plasma cells in the bone marrow. The estimated incidence rate in the United States is 7 per 100,000 persons, with approximately 32,270 new cases in 2020. The median overall survival (OS) is less than 7 years for patients with a revised International Staging System (r-ISS) stage II disease, and 3.6 years for patients with stage III disease. The median age at diagnosis is 69 years. With the aging population, the number of cases of MM is expected to continue to increase.

## Efficacy

Pepaxto® is a first-in-class peptide-drug conjugate (PDC) that targets aminopeptidases and rapidly releases alkylating agents into tumor cells. Melflufen is rapidly taken up by myeloma cells due to its high lipophilicity and is immediately hydrolyzed by peptidases to release an entrapped hydrophilic alkylator payload. Aminopeptidases are overexpressed in tumor cells and are even more pronounced in advanced cancers and tumors with a high mutational burden.

## NEW DRUG APPROVAL

Approval of Pepaxto® was based on results from a single-arm, open-label, Phase 2 study (HORIZON). Key trial results and study design are summarized in the tables below.

**Table 1. HORIZON (NCT02963493): Clinical Response Summary**

| | Pepaxto with Dexamethasone (N = 97) |
|---|---|
| Overall response rate (ORR), n (%) (95% confidence interval [CI]) | 23 (23.7) (15.7, 33.4) |
| Stringent complete response (sCR) | 0 |
| Complete response (CR) | 0 |
| Very good partial response (VGPR), n (%) | 9 (9.3) |
| Partial response (PR), n (%) | 14 (14.4) |
| Median duration of response in months (95% CI) | 4.2 (3.2, 7.6) |

**Source:** Pepaxto Prescribing Information

**Table 2. HORIZON (NCT02963493): Study Design, Safety, and Overall Results Summary**

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| **Study Population** | • 157 patients with RRMM who had received >2 prior lines of therapy and were exposed to an immunomodulator drug and a proteasome inhibitor, and were refractory to pomalidomide (Pomalyst) and/or daratumumab (Darzalex). Patients had TCR disease and/or EMD and/or high-risk cytogenetic features.<br>• 97 patients had TCR disease with ≥4 prior lines of therapy<br>• Patient characteristics:<br>  ○ 58% male<br>  ○ Median age: 65 years (range, 35–86 years)<br>  ○ ECOG performance status of 0–2: 0 (25%), 1 (59%), 2 (16%)<br>  ○ 41% with EMD<br>• 33% high-risk cytogenetics<br>• Median prior lines of therapy: 5 (range, 2–12) |

| Table 2. HORIZON (NCT02963493): Study Design, Safety, and Overall Results Summary | |
|---|---|
| **Interventions** | • <75 years of age: 40 mg melflufen IV on Day 1 + 40 mg dexamethasone on Days 1, 8, 15, and 22<br>• ≥75 years of age: 40 mg melflufen + 20 mg dexamethasone (same schedule as above)<br>Treatment was administered in 28-day cycles until either progressive disease or unacceptable toxicity. |
| **Endpoints** | • **Primary:** ORR<br>• **Secondary:** PFS, OS, DOR, time to response and time to progression |
| **Safety Results** | • Thrombocytopenia was reported in 99% of 157 patients. Grade 3 thrombocytopenia was reported in 26% and grade 4 thrombocytopenia was reported in 54% of patients.<br>• Neutropenia was reported in 95% of 157 patients. Grade 3 neutropenia was reported in 41% and grade 4 neutropenia was reported in 40% of patients. Febrile neutropenia was reported in 6% of patients.<br>• Anemia was reported in 84% of 157 patients. Grade 3 anemia was reported in 50% of 157 patients.<br>• The most common adverse reactions (>20%) were fatigue, nausea, diarrhea, pyrexia, and respiratory tract infection.<br>• The most commonly experienced non-hematologic toxicity that was grade 3 or 4 in severity was pneumonia (10%).<br>• Fatal infections were reported in <1% of 157 patients. Any-grade infection was reported in 58% of 157 patients. Grade 3 infections were reported in 20% and grade 4 infections were reported in 1.9% of patients. |
| **Efficacy Results** | • The ORR was 23.7% in the 97 heavily pretreated patients with RRMM; the median DOR in these patients was 4.2 months.<br>• Patients with EMD had an ORR of 41%.<br>• In patients who showed a response, the PFS was 8.5 months in the ITT population, 8.5 months in the patients with TCR disease, and 17.3 months in patients with EMD.<br>• Median OS in the ITT population was 11.6 months, 11.2 months in the TCR group, and 6.5 months in the EMD group.<br>• Median time to first response was 2.1 months (range, 1–6.1 months). |

**Source:** Pepaxto Prescribing Information

**Abbreviations:** DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; ITT, intent to treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma; TCR, triple-class refractory.

## Safety

### ADVERSE EVENTS

Most common adverse reactions (> 20%) are fatigue, nausea, diarrhea, pyrexia and respiratory tract infection. Most common laboratory abnormalities (≥50%) are leukocytes decrease, platelets decrease, lymphocytes decrease, neutrophils decrease, hemoglobin decrease, and creatinine increase.

### WARNINGS & PRECAUTIONS

**Thrombocytopenia:** Monitor platelet counts at baseline, during treatment, and as clinically indicated. Dose delay or dose reduction may be required to allow recovery of platelets.

**Neutropenia:** Monitor neutrophil counts at baseline, during treatment and as clinically indicated. Monitor patients with neutropenia for signs of infection. Dose delay or dose reduction may be required to allow recovery of neutrophils.

**Anemia:** Monitor red blood cell counts at baseline, during treatment, and as clinically indicated.

**Infections:** Fatal infections were reported in <1% of 157 patients who received Pepaxto® with dexamethasone. Any Grade infection was reported in 58% of 157 patients who received Pepaxto® and dexamethasone. Grade 3 infections were reported in 20% and Grade 4 infection was reported in 1.9% of patients. Respiratory tract infection occurred in 24% (Grade ≥3 in 5%), pneumonia in 13% (Grade ≥3 in 11%), and sepsis in 3.8% (Grade ≥3 in 3.2%) of patients [see Adverse Reactions (6.1)]. Consider antimicrobials as clinically appropriate.

**Increased Risk of Mortality with Pepaxto® at Dosages Higher than the Recommended Dosage:** Dosages exceeding the recommended dose for Pepaxto® may be associated with mortality.

**Secondary Malignancies:** Secondary malignancies such as myelodysplastic syndromes or acute leukemia have occurred in patients with multiple myeloma who have received Pepaxto®. Monitor patients long-term for the development of secondary malignancies.

**Embryo-Fetal Toxicity:** Based on its mechanism of action, Pepaxto® can cause fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Pepaxto® and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Pepaxto® and for 3 months after the last dose.

### CONTRAINDICATIONS

History of serious hypersensitivity reaction to melphalan flufenamide or melphalan.

## Clinical Pharmacology

### MECHANISMS OF ACTION

Melphalan flufenamide is a peptide conjugated alkylating drug. Due to its lipophilicity, melphalan flufenamide is passively distributed into cells and thereafter enzymatically hydrolyzed to melphalan. Similar to other nitrogen mustard drugs, crosslinking of DNA is involved in the antitumor activity of melphalan flufenamide. In cellular assays, melphalan flufenamide inhibited proliferation and induced apoptosis of hematopoietic and solid tumor cells. Additionally, melphalan flufenamide showed synergistic cytotoxicity with dexamethasone in melphalan resistant and non-resistant multiple myeloma cell lines.

## Dose & Administration

### ADULTS

Recommended dosage of Pepaxto® is 40 mg intravenously over 30 minutes on Day 1 of each 28-day treatment cycle, in combination with dexamethasone.

### PEDIATRICS

The safety and effectiveness of Pepaxto® have not been established in pediatric patients.

### GERIATRICS

Refer to adult dosing.

Of the 157 patients with RRMM who received Pepaxto®, 50% were 65 years and older, while 16% were 75 years and older. No overall differences in safety were observed between these patients and younger patients. Clinical studies of Pepaxto® in patients with RRMM did not include sufficient numbers of patients 65 years of age and older to determine if they respond differently from younger adult patients.

### RENAL IMPAIRMENT

No dose adjustment of Pepaxto® is recommended in patients with creatinine clearance (CrCl) 45 to 89 mL/min calculated using Cockcroft-Gault equation. Pepaxto® has not been studied in patients with CrCl 15 to 44 mL/min.

### HEPATIC IMPAIRMENT

No clinically meaningful differences in the PK of melphalan were observed based on age (35 to 85 years old), mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST).

## Product Availability

### DOSAGE FORM(S) & STRENGTH(S)

For injection: 20 mg melphalan flufenamide as a lyophilized powder in single-dose vial for reconstitution and dilution.