

PRODUCT PROFILER

PEPAXTO[®] (melphalan flufenamide)

INDICATION

PEPAXTO is an alkylating drug indicated in combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Limitations of Use

PEPAXTO is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials.

IMPORTANT SAFETY INFORMATION

PEPAXTO is contraindicated in patients with a history of serious allergic reaction to melphalan flufenamide or melphalan.

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COEUS Consulting Group, LLC

Sponsored by Oncopeptides, Inc

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This publication is designed for payers, formulary committees, or other similar entities with knowledge and expertise in the area of healthcare economics making decisions regarding access, coverage, and reimbursement for PEPAXTO[®].

Please see INDICATION and IMPORTANT SAFETY INFORMATION in the accompanying FULL PRESCRIBING INFORMATION.

Introduction

This Product Profiler introduces PEPAXTO® (melphalan flufenamide), a peptide-drug conjugate indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody.¹ PEPAXTO® received accelerated approval by the US Food and Drug Administration (FDA) on February 26, 2021 based on response rate.² PEPAXTO® is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials.

Patients with multiple myeloma (MM) experience a broad range of symptoms, which most commonly include anemia, renal insufficiency, hypercalcemia, bone lesions with bone

pain and fractures, fatigue, weight loss, and increased risk of infection.^{3,4} Despite recent advancements in treatment that have improved median survival, nearly all patients with MM eventually experience relapse and the disease remains incurable.^{5,6}

As the first approved peptide-drug conjugate, PEPAXTO® provides a novel mechanism of action, demonstrated clinical activity, and a manageable safety profile for patients with RRMM; in particular, heavily pretreated patients who typically require numerous, sequenced regimens may benefit from access to this additional therapeutic option. The following presents an overview of the disease state and the efficacy and safety considerations for the use of PEPAXTO®.

Disease State Overview

Multiple myeloma is a cancer of the bone marrow characterized by the accumulation of malignant plasma cells in the bone marrow, immunoglobulins in the blood or urine, and lytic bone lesions.⁷ In a healthy immune system, plasma cells are differentiated mature B-lymphocytes, a type of white blood cell that resides in the bone marrow and secretes immunoglobulins, or antibodies, in response to infection

(Figure 1).⁸ However, in MM, genetic abnormalities lead to the production of malignant plasma cells that replicate uncontrollably; disease symptoms may occur due to the crowding of the bone marrow with malignant cells or due to secretion of large quantities of nonfunctional monoclonal immunoglobulin protein in the blood and urine, which leads to organ damage.

Figure 1: Hematopoiesis and Plasma Cells

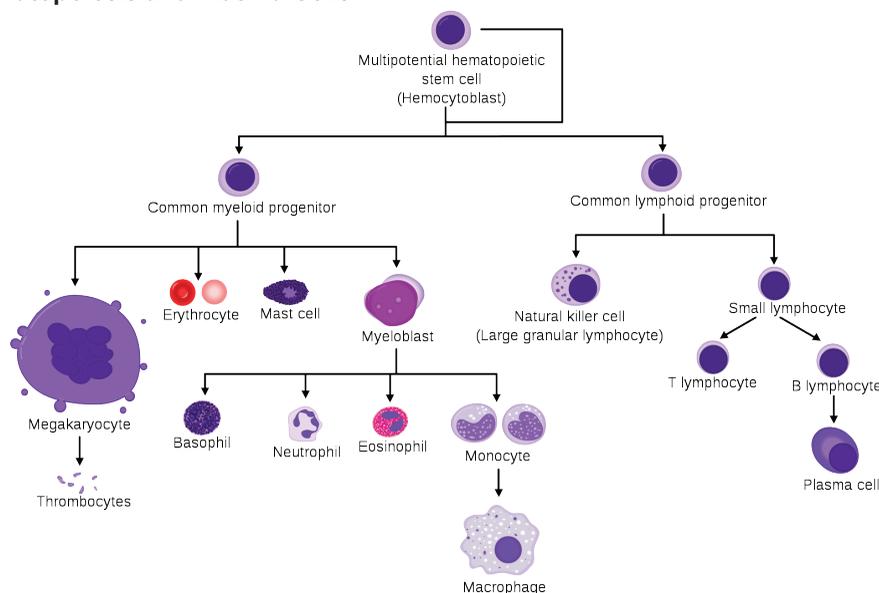


Image by A. Rad and M. Häggström. CC-BY-SA 3.0 license. https://commons.wikimedia.org/wiki/File:Hematopoiesis_simple.svg.

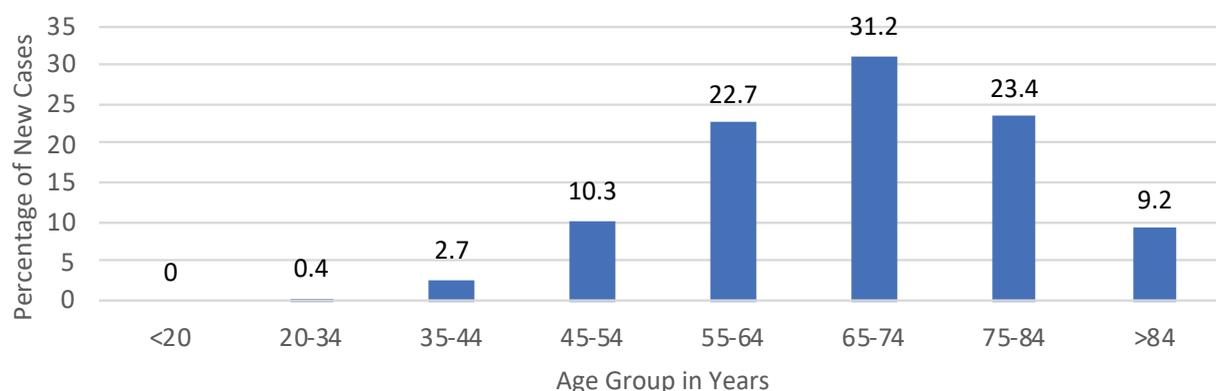
Incidence and prevalence

Multiple myeloma is the second most common hematologic malignancy⁹ accounting for 1%¹⁰ to 1.8%¹¹ of all cancers and 10% of all hematologic cancers.¹⁰ An estimated 149,956 people were living with MM in the United States (US) in 2018, and the incidence rate of MM is 7.1 per 100,000 with a higher rate in men than in women (8.8 vs 5.7 per 100,000, respectively).¹² Approximately 34,920 newly diagnosed cases and 12,410 deaths due to MM have been estimated to occur in 2021.¹² Approximately 56.5% of the prevalent MM population is estimated to have relapsed or refractory disease.¹³

Risk factors and prognosis

The risk of developing MM increases with age (Figure 2); the median age of diagnosis is 69 and diagnosis is rare in people younger than age 35.¹² Multiple myeloma occurs twice as frequently in African-Americans as in Whites.¹⁰ Additional risk factors are shown in Table 1.

Figure 2: Percentage of New Myeloma Cases by Age Group¹²



Modified from National Cancer Institute: <https://seer.cancer.gov/statfacts/html/mulmy.html>.

TABLE 1

Risk Factors for Multiple Myeloma^{14,15}

- Age
- Race
- Obesity
- Family history of multiple myeloma
- Prior history of monoclonal gammopathy of undetermined significance
- Prior history of solitary plasmacytoma
- Previous exposure to radiation or certain chemicals, pesticides, or herbicides

In the US, the 5-year relative survival rate in patients with metastatic MM is 54.5%.¹² Innovations and new approvals in therapies for MM have improved median overall survival (OS) rates; a recent analysis demonstrated an improved median OS from 3.9 years (patients diagnosed in 2004-2007) to 6.3 years (patients diagnosed in 2008-2012).¹⁶ Despite these advancements in treatment, nearly all patients with MM experience relapse, and the disease remains incurable.^{5,6}

Clinical Presentation

Diagnosis and Staging:

The diagnosis of MM is based on both pathologic and clinical findings (Table 2).¹⁰ There are three staging systems that have historically been used for MM: the Durie-Salmon staging system, the International Staging System (ISS), and the Revised ISS (R-ISS).¹⁷⁻¹⁹ The R-ISS is recommended as the preferred staging system per the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for multiple myeloma.¹⁸ This staging system correlates to prognosis as shown in Table 3.¹⁹

TABLE 2
International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma¹⁰

Both criteria must be met:

- Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma
- Any one or more of the following myeloma-defining events:
 - Evidence of end organ damage attributed to multiple myeloma; specifically:
 - Hypercalcemia
 - Renal insufficiency
 - Anemia
 - Bone lesions
 - Clonal bone marrow plasma cell percentage $\geq 60\%$
 - Serum free light chain ratio ≥ 100 mg/L
 - One or more focal lesions on magnetic resonance imaging studies

Modified from Rajkumar SV. *Am J Hematol.* 2020;95(5):548-567.

TABLE 3
International Staging System for Multiple Myeloma and Prognosis¹⁷⁻¹⁹

Stage	ISS	R-ISS	5-year OS by R-ISS Stage
I	Serum B2M < 3.5 mg/L and serum albumin ≥ 3.5 g/dL	ISS stage I and normal LDH, no high-risk cytogenetics ^a	82%
II	Neither stage I nor stage III	Neither stage I nor stage III	62%
III	Serum B2M ≥ 5.5 mg/L	ISS stage III and either elevated serum LDH or high-risk cytogenetics	40%

^aHigh-risk cytogenetics includes the presence of a translocation at t(4;14) or t(14;16) or the 17p deletion.

B2M=beta-2 microglobulin; ISS=International Staging System; LDH=lactate dehydrogenase; OS=overall survival; R-ISS=Revised International Staging System.

Symptoms:

Patients with MM most commonly present with the symptoms described by the CRAB acronym: hyper**C**alcemia, **R**enal insufficiency, **A**nemia, and/or lytic **B**one lesions (Table 4).³ Symptoms may also include bone pain, fractures, fatigue, weight loss, paresthesia, and fever.⁴ Additional complications include increased susceptibility to infection, elevated risk of venous thromboembolism, spinal cord compression, and hyperviscosity syndrome.^{8,20} Amyloidosis may occur, in

which excessive antibody proteins deposit throughout the body, including in fat, peripheral nerves, and organs such as the kidney and heart, leading to stiffening of tissues and loss of organ function.^{21,22} In extramedullary disease or plasmacytoma, plasma cells form outside the bone marrow as a consolidated tumor in the soft tissues of the body, with the most common sites including the upper part of the throat, tonsils, and sinus cavities.

TABLE 4
Symptoms and Complications of Multiple Myeloma^{3,4,8,20,21}

- Hypercalcemia
- Renal insufficiency
- Anemia
- Lytic bone lesions, bone pain, fractures
- Constitutional symptoms (fatigue, weight loss, fever)
- Paresthesias
- Increased susceptibility to infection
- Venous thromboembolism
- Spinal cord compression
- Hyperviscosity syndrome
- Amyloidosis
- Plasmacytoma

Treatment

Management of MM may include chemotherapy, novel targeted therapies, immunotherapy, biologic agents, stem cell transplant, and radiation therapy.²³ Radiation therapy

is primarily used for palliative treatment of bone lesions in cases of uncontrolled pain, imminent fracture, or spinal cord compression.¹⁸ Current classes of drugs used in regimens for the treatment of MM are listed in Table 5.

TABLE 5
Drugs Used in Multiple Myeloma^{10,18}

Proteasome Inhibitors	Histone Deacetylase Inhibitor
Bortezomib (Velcade®)	Panobinostat (Farydak®)
Carfilzomib (Kyprolis®)	Selective Inhibitor of Nuclear Export
Ixazomib (Ninlaro®)	Selinexor (Xpovio®)
Immunomodulatory Drugs	B-cell Maturation Antigen-Directed Antibody-Drug Conjugate
Lenalidomide (Revlimid®)	Belantamab mafodotin-blmf (Blenrep®)
Pomalidomide (Pomalyst®)	Chemotherapy
Thalidomide (Thalomid®)	Bendamustine (Bendeka®)
Anti-CD38 Monoclonal Antibodies	Cisplatin (Platinol®)
Daratumumab (Darzalex®)	Cyclophosphamide (Cytoxan®)
Daratumumab and hyaluronidase-fihj (Darzalex Faspro™)	Doxorubicin (Adriamycin®)
Isatuximab-irfc (Sarclisa®)	Etoposide (VePesid®)
SLAMF7 Monoclonal Antibody	Melphalan (Alkeran®)
Elotuzumab (Empliciti®)	CAR T Cell Therapy
Glucocorticoid	Idecabtagene vicleucel (Abecma®)
Dexamethasone (Decadron®)	

The first phase of treatment for patients with newly diagnosed MM is induction therapy; during this stage, the goal is to reduce the amount of disease.²² Treatment options include chemotherapy, targeted therapy, immunotherapy, and corticosteroids, and patients usually are treated with a combination regimen.²¹ The drugs chosen and duration of therapy depends on the patient’s age and comorbidities.

A young, fit patient who is eligible for autologous stem cell transplant (ASCT) will typically receive at least three to four cycles of induction therapy, followed by ASCT, and maintenance therapy with lenalidomide or a proteasome inhibitor.^{10,18} In patients who are not eligible for ASCT, induction therapy is administered continuously until disease progression occurs or followed by maintenance therapy.^{10,17,18}

Treatment of RRMM:

Almost all patients with MM who survive initial treatment will eventually relapse and require further therapy.¹⁰ After first relapse, ASCT may be considered if it was not utilized initially or in patients who relapse at least 18 months after transplant.^{10,17} There are many options for treatment regimens for patients with RRMM and no single standard of care; treatment should be individualized based on patient- and disease-related factors.¹⁷ Considerations include prior therapies received, patient response and tolerance of prior treatment, rate of disease progression and severity of symptoms, cytogenetic risk, presence of comorbidities or treatment toxicities, performance status, and patient preference. Indications, drug class, and routes for drugs used in regimens for the treatment of RRMM are detailed in Table 6.

Patients with RRMM that is triple-class refractory (TCR)—refractory to the three main classes of agents (proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies)—tend to have more aggressive disease with poorer response rates and survival outcomes.²⁴⁻²⁶ The approach to treatment for patients with TCR MM includes aggressive multi-agent regimens, chemotherapy, salvage ASCT, clinical trials, recycling previous regimens, and best supportive care.^{24,27} There is currently no standard of care for the treatment of patients with TCR MM.^{24,27} Therefore, there remains an unmet need for additional well-tolerated and effective treatment alternatives for the TCR MM population.

TABLE 6
PEPAXTO® and Select Therapeutic Options for Patients with RRMM

Drug	MOA	Manufacturer	FDA Approval	Route	Weight- ^a or BSA-based ^b Dosing	REMS Program	Indication(s)*
PEPAXTO® (melphalan flufenamide) ¹	PDC	Oncopeptides	2021	IV	No	No	<ul style="list-style-type: none"> RRMM (w/DEX) with ≥4 prior lines of therapy and refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb
Blenrep® (belantamab mafodotin-blmf) ²⁸	ADC	GlaxoSmithKline	2020	IV	Yes ^a	Yes	<ul style="list-style-type: none"> RRMM with ≥4 prior therapies including an anti-CD38 mAb, a PI, and an IMiD
Darzalex® (daratumumab) ²⁹	Anti-CD38 mAb	Janssen Biotech	2015	IV	Yes ^a	No	<ul style="list-style-type: none"> MM (w/LEN + DEX; BORT + MEL + PRED) newly diagnosed ineligible for ASCT MM (w/BORT + THAL + DEX) newly diagnosed eligible for ASCT RRMM (w/LEN + DEX) with ≥1 prior therapies MM (w/BORT + DEX) with ≥1 prior therapies; (w/POM + DEX) ≥2 prior therapies including LEN and a PI; (w/CARF + DEX) 1-3 prior lines of therapy; (monotherapy) ≥3 prior lines of therapy including a PI and an IMiD or double refractory to a PI and an IMiD

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Drug	MOA	Manufacturer	FDA Approval	Route	Weight ^a or BSA-based ^b Dosing	REMS Program	Indication(s)*
Darzalex Faspro® (daratumumab and hyaluronidase-fihj) ³⁰	Anti-CD38 mAb	Janssen Biotech	2020	SC	No	No	<ul style="list-style-type: none"> • MM (w/LEN + DEX; BORT + MEL + PRED) newly diagnosed ineligible for ASCT • MM (w/BORT + THAL + DEX) newly diagnosed eligible for ASCT • RRMM (w/LEN + DEX) with ≥1 prior therapies • MM (w/BORT + DEX) with ≥1 prior therapies • MM (monotherapy) with ≥3 prior lines of therapy including a PI and an IMiD or double refractory to a PI and an IMiD • AL newly diagnosed (w/ BORT + CYC + DEX)
Sarclisa® (isatuximab-irfc) ³¹	Anti-CD38 mAb	Sanofi-Aventis	2020	IV	Yes ^a	No	<ul style="list-style-type: none"> • MM (w/POM + DEX) with ≥2 prior therapies including LEN and a PI • RRMM (w/CAR + DEX) with 1-3 prior lines of therapy
Empliciti® (elotuzumab) ³²	Anti-SLAMF7 mAb	Bristol Myers Squibb	2015	IV	Yes ^a	No	<ul style="list-style-type: none"> • MM (w/LEN + DEX) with 1-3 prior therapies • MM (w/POM + DEX) with ≥2 prior therapies including LEN and a PI
Farydak® (panobinostat) ³³	HDAC inhibitor	Secura Bio	2015	PO	No	No	<ul style="list-style-type: none"> • MM (w/BORT + DEX) with ≥2 prior regimens including bortezomib and an IMiD
Kyprolis® (carfilzomib) ³⁴	PI	Amgen	2012	IV	Yes ^b	No	<ul style="list-style-type: none"> • RRMM (w/LEN + DEX; DEX; DAR + DEX) with 1-3 prior lines of therapy • RRMM (monotherapy) with ≥1 prior lines of therapy
Ninlaro® (ixazomib) ³⁵	PI	Takeda	2015	PO	No	No	<ul style="list-style-type: none"> • MM (w/LEN + DEX) with ≥1 prior therapies
Velcade® (bortezomib) ³⁶	PI	Takeda	2003	IV, SC	Yes ^b	No	<ul style="list-style-type: none"> • MM • MCL
Pomalyst® (pomalidomide) ³⁷	IMiD	Celgene	2013	PO	No	Yes	<ul style="list-style-type: none"> • MM (w/DEX) with ≥2 prior therapies including LEN and a PI • AIDS-related KS

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Drug	MOA	Manufacturer	FDA Approval	Route	Weight ^a or BSA-based ^b Dosing	REMS Program	Indication(s)*
Revlimid® (lenalidomide) ³⁸	IMiD	Celgene	2005	PO	No	No	<ul style="list-style-type: none"> • MM (w/DEX) • MM, as maintenance therapy after autologous HSCT • Anemia due to MDS • MCL • FL • MZL
Xpovio® (selinexor) ³⁹	SINE	Karyopharm Therapeutics	2019	PO	No	No	<ul style="list-style-type: none"> • MM (w/BORT + DEX) with ≥1 prior therapies • RRMM (w/DEX) with ≥4 prior therapies, and refractory to at least 2 PIs, 2 IMiDs and an anti-CD38 mAb • Relapsed or refractory DLBCL
Abecma® (idecabtagene vicleuce) ⁴⁰	CAR T	Bristol Myers Squibb	2021	IV	No	Yes	<ul style="list-style-type: none"> • RRMM (monotherapy) with ≥4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb

*Please reference individual products' full prescribing information for detailed information, including any Limitations of Use.

ADC=antibody-drug conjugate; AIDS=acquired immunodeficiency syndrome; AL=light chain amyloidosis; ASCT=autologous stem cell transplant; BORT=bortezomib; BSA=body surface area; CAR=chimeric antigen receptor; CARF=carfilzomib; CYC=cyclophosphamide; DAR=daratumumab; DLBCL=diffuse large B-cell lymphoma; DEX=dexamethasone; FL=follicular lymphoma; HDAC=histone deacetylase; HSCT=hematopoietic stem cell transplant; IMiD=immunomodulatory drug; IV=intravenous; KS=Kaposi sarcoma; LEN=lenalidomide; mAb=monoclonal antibody; MCL=mantle cell lymphoma; MDS=myelodysplastic syndrome; MEL=melphalan; MM=multiple myeloma; MOA=mechanism of action; MZL=marginal zone lymphoma; PDC=peptide-drug conjugate; PI=proteasome inhibitor; PO=orally; POM=pomalidomide; PRED=prednisone; RRMM=relapsed/refractory multiple myeloma; SINE=selective inhibitor of nuclear export; SC=subcutaneous; THAL=thalidomide.

PEPAXTO® Indication, Dosage, and Administration

Indication and Usage:

PEPAXTO® is a peptide-drug conjugate indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody.¹ This indication is approved under accelerated approval based on response rate.

Limitations of Use: PEPAXTO® is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials.

Dosage and Administration:

Dose: The recommended dose of PEPAXTO® is 40 mg administered intravenously over 30 minutes on Day 1 of each 28-day treatment cycle until disease progression or until unacceptable toxicity, in combination with dexamethasone.¹ The recommended dose of dexamethasone is 40 mg orally on Days 1, 8, 15, and 22 of each treatment cycle. For patients age 75 years or older, the recommended dose of dexamethasone is reduced to 20 mg.

Reconstitution and Dilution: PEPAXTO® should be reconstituted in 5% Dextrose Injection, USP, and subsequently diluted with 0.9% Sodium Chloride Injection, USP, to obtain a final concentration of 0.1 to 0.16 mg/mL. Determine the dose, the total volume of reconstituted PEPAXTO® solution required, and the number of PEPAXTO® vials needed. More than one vial may be needed for a full dose. Place PEPAXTO® vial(s) at room temperature for at least 30 minutes. Shake the vial(s) vigorously or vortex to disintegrate the lyophilized PEPAXTO® powder cake into a loose powder.

Aseptically reconstitute each vial with 40 mL of 5% Dextrose Injection, USP, to obtain a final concentration of 0.5 mg/mL. Ensure the 5% Dextrose Injection, USP, is at room temperature (20°C to 25°C/68°F to 77°F). Shake the vial(s) vigorously until solution is clear. Let the vial(s) stand to allow air bubbles to dissipate to confirm a clear solution.

Withdraw 80 mL from a refrigerated (2°C to 8°C/36°F to 46°F) 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP. Discard the withdrawn 80 mL. Withdraw the required volume of reconstituted solution from the PEPAXTO® vial(s) and transfer into the bag containing 0.9% Sodium Chloride Injection, USP, to obtain a final concentration of 0.1 to 0.16 mg/mL. Discard any unused portion left in the vial(s). Gently invert the bag to mix the solution. Do not shake the bag and check that the PEPAXTO® solution is clear and colorless to pale yellow. Do not use if solution discoloration or particles are observed.

Reconstitution and dilution steps must be completed within 30 minutes.

Administration: The solution should be administered as a 30-minute intravenous infusion via a central venous access device, with infusion starting within 30 minutes of removing the diluted PEPAXTO® solution from the refrigerator or within 60 minutes of start of reconstitution.

If not used for immediate administration, the diluted PEPAXTO® solution may be stored in a refrigerator within 30 minutes after initial reconstitution and stored for up to 6 hours. Upon completion of infusion, flush the central catheter per individual institution guidelines.

Dosage Form and Strength:

Intravenous injection: PEPAXTO® comes in a single use vial containing 20 mg of melphalan flufenamide as a sterile lyophilized white to off-white powder for reconstitution and dilution.¹

How Supplied and Storage Conditions:

PEPAXTO® is supplied in a 50-mL single dose vial as a white to off-white lyophilized powder containing 20 mg melphalan flufenamide for reconstitution. (After reconstitution, the solution is clear and colorless to light yellow.)¹ Each 20 mg vial is packaged in a single carton (NDC 73657-020-01). PEPAXTO® should be stored at 2°C to 8°C (36°F to 46°F), protected from light, and retained in its original carton until use.

PEPAXTO® Chemistry and Clinical Pharmacology

Chemical and Physical Properties:

PEPAXTO® is an alkylating drug with chemical name Ethyl (2S)-2-[[[(2S)-2-amino-3-[4-[bis(2-chloroethyl)amino]phenyl]propanoyl]amino]-3-(4-fluorophenyl)propanoate hydrochloride.¹ Molecular weight of the compound is 498.4 as the free base and 534.9 as the hydrochloride salt. Melphalan flufenamide hydrochloride is soluble in most organic solvents, while sparsely soluble in aqueous solutions, with a pKa of 7.13. Each vial of PEPAXTO® contains a sterile, white to off-white lyophilized powder with 20 mg melphalan flufenamide and 1000 mg sucrose.

Clinical Pharmacology and Mechanism of Action:

Due to its lipophilicity, melphalan flufenamide is passively distributed into cells, where it is enzymatically hydrolyzed

to melphalan.¹ Cross-linking of DNA is involved in the anti-tumor 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. Melphalan flufenamide peak plasma concentrations are reached during the 30-minute infusion, with active metabolite plasma concentrations reaching peak 4 to 15 minutes after the end of the infusion of PEPAXTO® 40 mg. After the end of the infusion, melphalan flufenamide is eliminated from plasma with a mean half-life of 2.1 minutes and its active metabolite melphalan with a mean half-life of 70 minutes.

PEPAXTO® Efficacy Outcomes

The efficacy of PEPAXTO® in combination with dexamethasone was evaluated in HORIZON [NCT02963493], a multicenter, single-arm, open-label phase 2 trial.⁴¹ A total of 157 patients with RRMM who had received at least two prior lines of therapy, including an immunomodulatory drug and a proteasome inhibitor, and were refractory to pomalidomide and/or an anti-CD38 monoclonal antibody were enrolled.⁴¹ Efficacy data supporting the labeled indication is based on a subset of 97 patients who had received four or more prior lines of therapy and were refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Participants received PEPAXTO® 40 mg on Day 1 and dexamethasone 40 mg orally (20 mg for patients ≥75 years

of age) on Day 1, 8, 15, and 22 of each 28-day cycle until disease progression or unacceptable toxicity. Of the 97 patients reported, the median age was 65 years (range: 35-86 years); 58% were male, 87% were White, and 6% were Black or African American. Additional baseline characteristics are shown in Table 7.

The major efficacy outcome measures were overall response rate and duration of response, assessed according to the International Myeloma Working Group Criteria. Efficacy results in the 97 patients supported the FDA approval of PEPAXTO® and are provided in Table 8. Efficacy results in a subset of 40 patients with extramedullary disease from the 97 patients are shown in Table 9.

TABLE 7

Disease Characteristics¹

Parameter	PEPAXTO® with Dexamethasone (N=97)
Years from diagnosis to start of PEPAXTO®, median (range)	6.4 (2.1 to 24.6)
Prior treatment regimens, median (range)	6 (4 to 12)
Documented refractory status, (%)	
Lenalidomide	94
Pomalidomide	92
Bortezomib	74
Carfilzomib	63
Daratumumab	93
Alkylator refractory, (%)	75
Previous stem cell transplant, (%)	70
International Staging System at Baseline, (%)	
I	30
II	32
III	34
Missing/Unknown	4
High-risk cytogenetics ^a , (%)	33
Extramedullary disease (EMD), (%)	41

^adel(17p), t(4;14), t(14;16), gain (1q) and t(14;20) at study entry.

TABLE 8

Efficacy Results in Indicated Patient Population^{1,42}

	PEPAXTO® with Dexamethasone (N=97)
Overall response rate (ORR), % [95% CI]	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]
Median time to first response in months (range)	2.1 (1.0 to 6.1)
Median progression-free survival in months [95% CI]	3.8 [3.0, 4.6]
Median overall survival in months [95% CI] ^a	9.1 [6.4, 11.5]

^aFrom Oncopeptides data on file.

TABLE 9
Efficacy Results in Patients with EMD⁴²

	PEPAXTO® with Dexamethasone (N=40)
Overall response rate (ORR), % [95% CI]	15.0 [5.7, 29.8]
Stringent complete response (sCR)	0
Complete response (CR)	0
Very good partial response (VGPR), n (%)	3 (7.5)
Partial response (PR), n (%)	3 (7.5)
Median duration of response in months [95% CI]	3.9 [1.8, NA]
Median time to first response in months (range)	2.8 (1.0 to 5.9)
Median progression-free survival in months [95% CI]	2.9 [1.9, 3.7]
Median overall survival in months [95% CI]	5.8 [5.0, 9.1]

EMD=extramedullary disease; NA=not available.

PEPAXTO® Safety Considerations

PEPAXTO® Safety Results:

The safety data reflect exposure to PEPAXTO® in combination with dexamethasone in 157 adult patients with RRMM treated with PEPAXTO® and dexamethasone in the clinical trial HORIZON.¹ Among patients in the trial who received PEPAXTO®, 29% were exposed for 6 months or longer and 6% were exposed for greater than 1 year.

Adverse Reactions:

The most common adverse reactions associated with PEPAXTO® (>20%) are fatigue, nausea, diarrhea, pyrexia, and respiratory tract infection.¹ The most common laboratory abnormalities (≥50%) include a decrease in leukocytes, platelets, lymphocytes, neutrophils, and hemoglobin and an increase in creatinine. Adverse reactions reported in at least 10% of patients and laboratory abnormalities reported in more than 50% of patients treated with PEPAXTO® and dexamethasone are presented in Table 10 and 11, respectively.

TABLE 10
Adverse Reactions (≥10%) in Patients with RRMM Who Received PEPAXTO® with Dexamethasone¹

Adverse Reaction	PEPAXTO® with Dexamethasone (N=157)	
	All Grades (%)	Grade 3 or 4 (%)
<i>General disorders and administration site disorders</i>		
Fatigue ^a	55	6
Pyrexia ^b	24	1.9
Edema peripheral ^b	14	1.3
<i>Gastrointestinal disorders</i>		
Nausea ^b	32	0.6
Diarrhea	27	0
Constipation ^b	15	0.6
Vomiting	13	0
<i>Infections</i>		
Respiratory tract infection ^{b,c}	24	5
Pneumonia ^d	13	11
<i>Respiratory, thoracic, and mediastinal disorders</i>		
Cough ^b	17	0
Dyspnea ^b	11	1.3
Dyspnea exertional	10	0
<i>Metabolism and nutrition disorders</i>		
Decreased appetite ^b	14	0.6
Hypokalemia ^b	14	1.3
Hypocalcemia ^b	10	0.6
<i>Nervous system disorders</i>		
Headache	13	0
Dizziness	11	0
<i>Musculoskeletal and connective tissue disorders</i>		
Bone pain ^b	13	1.9
Pain in extremity ^b	13	1.9
Back pain ^b	12	0.6
Arthralgia	10	0

Adverse Reaction	PEPAXTO® with Dexamethasone (N=157)	
	All Grades (%)	Grade 3 or 4 (%)
Psychiatric disorders Insomnia ^b	11	0.6

^aFatigue includes fatigue and asthenia.

^bNo Grade 4 adverse reactions occurred.

^cRespiratory tract infection includes upper respiratory tract infection, lower respiratory tract infection, respiratory tract infection, and respiratory tract infection viral.

^dPneumonia includes pneumonia, *Pneumocystis jirovecii* pneumonia, and pneumonia viral.

RRMM=relapsed or refractory multiple myeloma.

Clinically relevant adverse reactions in <10% of patients who received PEPAXTO® in combination with dexamethasone (N=157) included hypersensitivity reaction (7%),

febrile neutropenia (6%), sepsis (3.8%), and Grade 3 or 4 hemorrhages (3.8%).

TABLE 11
Laboratory Abnormalities (≥50%) that Worsened from Baseline¹

Laboratory Abnormality	PEPAXTO® with Dexamethasone ^a	
	All Grades (%) ^b	Grade 3 or 4 (%) ^c
Leukocytes decrease	99	88
Platelets decrease	99	80
Lymphocytes decrease	97	95
Neutrophils decrease	95	82
Hemoglobin decrease	84	50
Creatinine increase	68	1 ^d

^aDenominators for percentages are the number of patients with assessments at baseline and post-baseline (N=157 for all abnormalities).

^bPatients with any worsening grade.

^cPatients with worsening to Grade 3 or 4, respectively.

^dNo Grade 4 laboratory abnormality occurred.

Permanent discontinuation of PEPAXTO® due to an adverse reaction occurred in 22% of patients; the only cause of discontinuation attributed to more than 3% of patients was thrombocytopenia (11%).¹ Dosage interruptions of PEPAXTO® due to an adverse reaction occurred in 62% of patients. The adverse reactions that resulted in dosage interruption of PEPAXTO® in more than 3% of patients included thrombocytopenia (43%), neutropenia (29%), anemia (10%), respiratory tract infection (7%), leukopenia (6%), and pyrexia (4.5%). Dose reductions of PEPAXTO® due to an adverse reaction occurred in 27% of patients; causes occurring in more than 3% of patients were thrombocytopenia (22%) and neutropenia (6%).

Serious adverse reactions occurred in 49% of patients who received PEPAXTO®; the most common occurring in more than 3% of patients were pneumonia (10%), respiratory tract infection (6%), thrombocytopenia (5%), febrile neutropenia (5%), and sepsis (3.2%).¹ Fatal adverse reactions occurred in 10 patients (6%) who received PEPAXTO®; general physical health deterioration (1.9%) and respiratory failure (1.3%) represented more than 1%.

For patients experiencing nausea, consider providing a serotonin-3 (5-HT₃) receptor antagonist or other antiemetic prior to and during treatment with PEPAXTO®.

For patients experiencing myelosuppression (platelet count $<50 \times 10^9/L$ or absolute neutrophil count $<1 \times 10^9/L$ on an intended PEPAXTO® dosing day), withhold PEPAXTO® and monitor blood counts until platelet count $\geq 50 \times 10^9/L$ or absolute neutrophil count $\geq 1 \times 10^9/L$. Resume PEPAXTO® at the same dose if delay is 2 weeks or less or at one dose level lower if delay is more than 2 weeks. For a Grade 4 hematologic adverse reaction on an intended PEPAXTO® dosing day in 2 consecutive cycles, resume PEPAXTO® at one dose level lower.

For patients experiencing Grade 2 non-hematologic adverse reactions, consider withholding PEPAXTO® until resolved to at least Grade 1 or baseline, and consider resuming at one dose level lower. For patients experiencing Grade 3 or 4 non-hematologic adverse reactions, withhold PEPAXTO® until resolved to at least Grade 1 or baseline, and resume at one dose level lower, as clinically appropriate.

Contraindications:

History of serious hypersensitivity reaction to melphalan flufenamide or melphalan.¹

Warnings and Precautions:

Thrombocytopenia: Thrombocytopenia was reported in 99% of 157 patients who received PEPAXTO® with dexamethasone.¹ Grade 3 thrombocytopenia was reported in 26% and Grade 4 thrombocytopenia was reported in 54% of patients. Thrombocytopenia may lead to hemorrhage. Any Grade hemorrhage was reported in 28% of 157 patients. Grade 3 hemorrhage was reported in 3.2% and Grade 4 hemorrhage was reported in $<1\%$ of patients. Grade 3 or 4 thrombocytopenia occurred in 43% of patients during the first cycle, with a median time to onset of 15 days from the first dose.

Monitor platelets at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first 2 months of treatment with PEPAXTO®. Do not administer PEPAXTO® if the platelet count is less than $50 \times 10^9/L$. Withhold PEPAXTO® until platelet count is $50 \times 10^9/L$ or greater and resume at the same or a reduced dose based on duration of interruption. Adjust dose and/or dose schedule based on signs and symptoms of bleeding.

Neutropenia: Neutropenia was reported in 95% of 157 patients who received PEPAXTO® with dexamethasone.¹ 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. Neutropenia may lead to infection. Grade 3 or 4 neutropenia occurred in 50% of patients during the first cycle, with a median time to onset of 15 days from the first dose.

Monitor neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first 2 months of treatment with PEPAXTO®. Do not administer PEPAXTO® if absolute neutrophil count is less than $1 \times 10^9/L$. Withhold PEPAXTO® until absolute neutrophil count is $1 \times 10^9/L$ or greater and resume at the same or a reduced dose based on duration of interruption. Consider leukocyte growth factor as clinically appropriate.

Anemia: Anemia was reported in 84% of 157 patients who received PEPAXTO® with dexamethasone.¹ Grade 3 anemia was reported in 50% of 157 patients.

Monitor red blood cell counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first 2 months of treatment. Treat anemia as clinically indicated and as per standard guidelines. Dosage modification and dose delay of PEPAXTO® may be required to allow recovery of blood cell counts.

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.¹ Grade 3 infections were reported in 20% and Grade 4 infections were 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. Consider antimicrobials as clinically appropriate.

Increased Risk of Mortality with PEPAXTO® at Dosages Higher than the Recommended Dosage: A nonclinical safety study in dogs with melphalan flufenamide at dosages exceeding the recommended dose for relapsed and refractory multiple myeloma was associated with mortality.¹ There is limited clinical experience of PEPAXTO® at dosages higher than recommended. The safety and efficacy of PEPAXTO® has not been established for use as a conditioning regimen in patients receiving transplant.

Secondary Malignancies: Secondary malignancies such as myelodysplastic syndromes or acute leukemia have occurred in patients with multiple myeloma who have

received PEPAXTO®.¹ 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 growing cells.¹ 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 a female partner of reproductive potential to use effective contraception during treatment with PEPAXTO® and for 3 months after the last dose.

Use in Specific Populations:

Geriatric Use:

Of the 157 patients with RRMM who received PEPAXTO®, 50% were 65 years and older, while 16% were 75 years and older.¹ 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 (CL_{cr}) 45 to 89 mL/minute calculated using the Cockcroft-Gault equation.¹ PEPAXTO® has not been studied in patients with CL_{cr} 15 to 44 mL/minute.

P&T Committee Considerations

Multiple Myeloma Disease Burden

Innovations and approvals of novel therapies for MM have improved survival rates for patients over the last two decades.¹⁶ However, nearly all patients with MM still experience relapse and the disease remains incurable.⁵ Multiple myeloma is expected to cause 12,410 deaths in the United States in 2021.¹² Historical data demonstrate that once disease relapses, the depth of response, progression-free survival (PFS), and overall survival (OS) decline with each subsequent line of therapy received.⁴³ In a registry study of patients with MM treated between 2008 and 2013, the median OS for patients receiving first-, second-, third-, and fourth-line therapy was 37.5 months, 19.7 months, 13.9 months, and 9.2 months, respectively.

According to the American Society of Clinical Oncology's (ASCO) treatment guidelines for MM, there are many options for treatment regimens for patients with relapsed and/or refractory multiple myeloma (RRMM), and treatment should be individualized based on patient-related, disease-related, and treatment-related factors.¹⁷ The ASCO guidelines note that patients may receive multiple lines of therapy for relapsed disease, and the optimal sequencing of these regimens is unknown.

Choosing a treatment for MM becomes more challenging with each subsequent line of therapy.^{24,44} With each relapse, there is a decrease in the number of treatment options that remain, patient ability to tolerate therapies, response rates to available treatments, and median time to disease progression.^{24,44}

Patients with RRMM have high direct and indirect costs associated with disease management.⁴⁵ Over a 12-month period, total costs for patients with RRMM have been estimated to range from \$93,683 to \$315,296, depending on the medications utilized.⁴⁵ Estimates factored in costs associated with laboratory testing, treatment-related fees, drug pricing, premedication, medical visits, and indirect costs. Treatment for advanced disease may be associated with higher costs than initial therapy. Multiple studies have shown increased total healthcare costs with later lines of therapy than with first-line therapy for MM.^{46,47} A large retrospective claims analysis of Truven MarketScan® Commercial and Medicare databases, which included over 11,000 patients with MM who were diagnosed between 2006 and 2016 and received treatment, demonstrated that disease progression is associated with higher healthcare

utilization.⁴⁸ Compared to patients with stable disease, patients with disease progression had higher hospitalization rates, outpatient visits, and total annual healthcare costs.

Clinical Considerations for PEPAXTO®

PEPAXTO® is a peptide-drug conjugate that received accelerated approval by the FDA in February 2021 for use in combination with dexamethasone for the treatment of adult patients with RRMM who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody.¹ PEPAXTO® is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials.

As a peptide-drug conjugate, PEPAXTO® leverages aminopeptidases, which are overexpressed in MM cells, and are further amplified as disease progresses and relapses.^{49,50} PEPAXTO® is taken up by myeloma cells due to its lipophilicity and is metabolized by aminopeptidases to release the cytotoxic melphalan component once inside the tumor cell. PEPAXTO® circumvents the development of transporter-associated resistance through its passive uptake into cells.⁴¹

The approval of PEPAXTO® provides a new therapeutic option for patients with RRMM who typically require numerous, sequenced regimens and may run out of potential treatment options. Data support anti-tumor activity in patients who received at least four prior lines and were refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and a CD38-directed monoclonal antibody.¹ This population includes heavily pretreated triple-class refractory patients with poor prognosis factors.^{1,24}

The HORIZON trial demonstrated an overall response rate of 24% and a median duration of response of 4.2 months with PEPAXTO® in combination with dexamethasone in 97 patients who were treated with at least four prior lines of therapy and were refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and a CD38-directed monoclonal antibody.¹

In the HORIZON study, the safety profile of PEPAXTO® plus dexamethasone consisted primarily of hematologic adverse reactions that were managed with dose modifications and supportive care.¹ Hematologic adverse events accounted for most Grade 3/4 adverse events and included

thrombocytopenia (43%) and neutropenia (50%) occurring during the first cycle, with a median time to onset of 15 days from the first dose. Sequelae from these toxicities included Grade 3/4 bleeding events in 3.8% of patients and febrile neutropenia in 6% of patients, respectively. Neutropenia may lead to infection.

The most frequent non-hematologic adverse events were infections, Grade 3 (20%) and Grade 4 (1.9%). Fatal infections were reported in <1%. The most common type of infections were pneumonia (11%) and respiratory tract infection (5%). Grade 3 or 4 fatigue occurred in 6% of patients.

Treatment considerations for PEPAXTO® include monitoring of complete blood count, particularly for neutrophil, red blood cell, and platelet counts, at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months. Consider providing a serotonin-3 (5-HT₃) receptor antagonist or other antiemetic prior to and during treatment with PEPAXTO®.¹

Melphalan flufenamide (PEPAXTO®) with dexamethasone is included in the NCCN Guidelines as a category 2A option for patients with previously treated MM who meet the labeled indication.¹⁸

Cost and Access Considerations for PEPAXTO®

The cost of PEPAXTO® and select drugs indicated for RRMM appear in Table 12. These prices reflect the wholesale acquisition cost, current as of July 8, 2021, and only reflect costs of individual drugs, not combination regimens.⁵¹ The 28-day costs range from \$8,549.33 to \$23,812.65 when averaged over the first four 28-day cycles of therapy and assuming an 80 kg body weight or 1.8 m² body surface area (excluding Abecma® as it's administered as a single dose). For some agents with weight-based dosing, the costs are higher if the patient's body weight exceeds 80 kg. For example, with Blenrep®, an additional 100 mg vial would need to be used, increasing the cost by 50%. Excluding Abecma®, median 28-day cost of the listed therapies is \$19,000, which is the 28-day cost of PEPAXTO®.

A budget impact model (BIM) for PEPAXTO® has been developed to allow health care plans to assess the budgetary impact of adopting PEPAXTO® in the FDA-indicated patient population into its formulary.⁵² In addition to patient population and market share of standard of care triple-class refractory RRMM therapies, the BIM framework takes into consideration prior lines of therapy, therapy costs, monitoring costs, and adverse event costs. The model considers two main scenarios - with and without PEPAXTO® adoption. Additionally, the BIM supports the estimation of budgetary

impact in two market share scenarios: a short-term estimate, representative of market uptake for PEPAXTO® after approximately 1 year, and a peak estimate, representative of market uptake after approximately 3 years from launch of product. Comparing the total costs of treating patients with triple-class refractory RRMM with at least four prior lines of therapy in each of these scenarios allows the health plan to assess the total, per member per month (PMPM), and per patient per month (PPPM) budgetary impacts of PEPAXTO® adoption.

The model assumes a health plan size of 1,000,000 members, with an estimated 13 of those being patients with triple-class refractory RRMM treated with at least four prior lines of therapy. Over a 1-year time horizon, prior to the adoption of PEPAXTO®, the total cost of treating patients with triple-class refractory RRMM with at least four prior lines of therapy is \$3,694,856. With the introduction of PEPAXTO® in the short-term market uptake scenario, the total cost is \$3,678,551, which translates to a savings of \$16,306 and a reduction in the PMPM by -\$0.001. In the peak market uptake scenario, the total cost is \$3,670,117, resulting in a difference of -\$0.002 PMPM and a savings of \$24,739 from current to 3-4 years in the future. The results are sensitive to the following parameters for PEPAXTO®: relative time on treatment and drug cost.

The model is not intended to compare directly the efficacy of various treatment regimens with each other, and cannot be generalizable to other patient populations, as it is based on clinical trial data specific to PEPAXTO® and other therapies within the triple-class refractory with at least four prior lines of therapy RRMM treatment space. Additionally, the model only considers costs associated with drug acquisition, therapy, monitoring, and Grade 3 and 4 adverse events.

The increase in use of PEPAXTO® from a payer perspective for the treatment of patients with triple-class refractory RRMM with at least four prior lines of therapy is expected to result in cost savings across monitoring and adverse event costs from a total payer perspective. The model shows a decrease in cost at both short-term and peak market adoption of PEPAXTO® for the treatment of triple-class refractory RRMM with at least four prior lines of therapy, at approximately 0.4% increase in the first year of adoption. Cost decrease could be attributed to PEPAXTO® taking market share from therapies with higher acquisition and administration costs. A one-way sensitivity analysis demonstrated that the relative time on treatment could result in cost savings. The analysis demonstrated that the budget impact results were robust across not only the duration of treatment, but also per package cost of PEPAXTO® and the percent short-term market uptake for PEPAXTO®.

TABLE 12

Cost of PEPAXTO® and Select Products Indicated for RRMM, as of July 8, 2021⁵¹

MOA	Drug	Dosing*	Cost per unit	28-day cost ^{a,b}	1-year cost ^a
PDC	PEPAXTO® (melphalan flufenamide) ¹	40 mg on Day 1 of 28-day cycles ¹	\$9,500.00 per 20 mg vial	\$19,000.00	\$247,000.00
ADC	Blenrep® (belantamab mafodotin-blmf) ²⁸	2.5 mg/kg once every 3 weeks ²⁸	\$8,401.16 per 100 mg vial	\$22,403.09 (>40-80 kg)	\$291,240.21 (>40-80 kg)
				\$33,604.64 (>80-120 kg)	\$436,860.32 (>80-120 kg)
Anti-CD38 mAb	Darzalex® (daratumumab) ²⁹	16 mg/kg once weekly for the first 8 weeks, then every 2 weeks for weeks 9-24, then every 4 weeks ²⁹	\$582.35 per 100 mg/5 mL vial	\$22,711.65 (>75-81 kg)	\$174,122.65 (>75-81 kg)
	Darzalex Faspro™ (daratumumab and hyaluronidase-fihj) ³⁰	1,800 mg/30,000 units once weekly for the first 8 weeks, then every 2 weeks for weeks 9-24, then every 4 weeks ³⁰	\$7,937.55 per 1,800-30,000 mg-unit/15 mL vial	\$23,812.65	\$182,563.65
	Sarclisa® (isatuximab-irfc) ³¹	10 mg/kg every week for 4 weeks followed by every 2 weeks ³¹	\$666.25 per 100 mg/5 mL vial	\$13,325.00 (>70-80 kg)	\$149,240.00 (>70-80 kg)
Anti-SLAMF7 mAb	Empliciti® (elotuzumab) ³²	10 mg/kg every week for the first 8 weeks, then every 2 weeks ³²	\$2,667.53 per 400 mg vial	\$16,005.18 (>70-80 kg)	\$160,051.80 (>70-80 kg)
				\$18,005.82 (>80-90 kg)	\$180,058.28 (>80-90 kg)
HDAC inhibitor	Farydak® (panobinostat) ³³	20 mg on Days 1, 3, 5, 8, 10, and 12 of Weeks 1 and 2 of 21-day cycle ³³	\$2,816.50 per 20 mg capsule	\$18,776.68	\$244,096.84
IMiD	Pomalyst® (pomalidomide) ³⁷	4 mg once daily on Days 1-21 of 28-day cycle ³⁷	\$907.61 per 4 mg capsule	\$19,059.78	\$247,777.15
	Revlimid® (lenalidomide) ³⁸	25 mg once daily on Days 1-21 of 28-day cycle ³⁸	\$797.34 per 25 mg capsule	\$16,744.23	\$217,675.02
PI	Kyprolis® (carfilzomib) ³⁴	Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle at 20 mg/m ² for first 2 doses, then 56 mg/m ² ³⁴	\$2,579.11 per 60 mg vial	\$20,632.88	\$268,227.44
	Ninlaro® (ixazomib) ³⁵	4 mg on Days 1, 8, and 15 of 28-day cycle ³⁵	\$3,633.00 per 4 mg capsule	\$10,899.00	\$141,687.00

PRODUCT PROFILER: PEPAXTO® (melphalan flufenamide)

MOA	Drug	Dosing*	Cost per unit	28-day cost ^{a,b}	1-year cost ^a
PI	Velcade® (bortezomib) ³⁶	1.3 mg/m ² /dose on Days 1, 4, 8, and 11 of 21-day cycle ³⁶	\$1,603.00 per 3.5 mg vial	\$8,549.33	\$83,356.00
SINE	Xpovio® (selinexor) ³⁹	80 mg on Days 1 and 3 of each week ³⁹	\$23,078.00 per 28-day therapy pack (32 20-mg tablets)	\$23,078.00	\$300,014.00
CAR T	Abecma® (idecabtagene vicleucel) ⁴⁰	Single dose of chimeric antigen receptor (CAR)-positive T cells in one or more infusion bags ⁴⁰	\$419,500.00 per unit dose	\$419,500.00	\$419,500.00

*Please reference individual products' full prescribing information for detailed dosing information.

Costs reflect the wholesale acquisition cost, current as of July 8, 2021. Costs are only for individual drugs, not combination regimens. Calculations account for waste from single-use vials.

^aCalculations assume 80 kg body weight and 1.8 m² body surface area. For weight-based dosing calculations, an additional row represents the calculated cost if body weight exceeds 80 kg and an additional vial is needed.

^b28-day cost based on average of first four 28-day cycles of therapy. Time frame selected due to average duration of therapy of PEPAXTO® in the HORIZON trial.

ADC=antibody drug conjugate; CAR=chimeric antigen receptor; HDAC=histone deacetylase; IMiD=immunomodulatory drug; mAb=monoclonal antibody; MOA=mechanism of action; PDC=peptide-drug conjugate; PI=proteasome inhibitor; RRMM=relapsed or refractory multiple myeloma; SINE=selective inhibitor of nuclear export.

PEPAXTO® is available via the following specialty distributors: McKesson Specialty Health, McKesson Plasma and Blood, AmerisourceBergen Specialty Distributor, Oncology Supply, and Cardinal Specialty Health. PEPAXTO® is available through two specialty pharmacies: onco360 and Biologics. The ON COURSE™ program offers eligible patients the following support: benefits investigation, prior authorization facilitation and appeals support, commercial copay assistance program, patient assistance program, and patient and caregiver support resources (<https://oncoursupport.com>).

CONCLUSION

Multiple myeloma is an incurable hematologic malignancy with significant clinical and economic burden. Multiple myeloma becomes more challenging with each subsequent line of therapy.^{24,44} With each relapse, there is a decrease in the number of treatment options that remain, patient ability to tolerate therapies, response rates to available treatments, and median time to disease progression.^{24,44} Additionally, total healthcare costs increase with later lines of therapy than with first-line therapy for MM.^{46,47}

PEPAXTO® is a novel peptide-drug conjugate that is indicated in combination with dexamethasone for the treatment of adult patients with RRMM who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody. This indication is approved under accelerated approval based on response rate. PEPAXTO® is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials. Clinical data have shown that PEPAXTO® with dexamethasone has demonstrated efficacy responses and a manageable safety profile for patients with heavily pretreated RRMM, including patients who are refractory to alkylating agents. Management of RRMM requires access to numerous treatment options since patients typically receive multiple sequenced regimens over the course of their disease. PEPAXTO® provides access to another treatment option for patients.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PEPAXTO safely and effectively. See full prescribing information for PEPAXTO.

PEPAXTO® (melphalan flufenamide) for injection, for intravenous use

Initial U.S. Approval: 2021

INDICATIONS AND USAGE

PEPAXTO is an alkylating drug indicated in combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. (1)

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1)

Limitations of Use: PEPAXTO is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials. (1, 5.5)

DOSAGE AND ADMINISTRATION

- Recommended dosage of PEPAXTO is 40 mg intravenously over 30 minutes on Day 1 of each 28-day treatment cycle, in combination with dexamethasone. (2.1)
- See Full Prescribing Information for instructions on preparation and administration. (2.4)

DOSAGE FORMS AND STRENGTHS

For injection: 20 mg melphalan flufenamide as a lyophilized powder in single-dose vial for reconstitution and dilution. (3)

CONTRAINDICATIONS

History of serious hypersensitivity reaction to melphalan flufenamide or melphalan. (4)

WARNINGS AND 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. (2.3, 5.1)
- 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. (2.3, 5.2)
- Anemia:** Monitor red blood cell counts at baseline, during treatment, and as clinically indicated. (5.3)
- Infections:** Monitor for signs/symptoms of infection and treat promptly. (5.4)
- 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. (1, 5.5, 13.2)
- Secondary Malignancies:** Monitor patients long-term for the development of secondary malignancies. (5.6)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (> 20%) are fatigue, nausea, diarrhea, pyrexia and respiratory tract infection. (6.1)
Most common laboratory abnormalities (≥50%) are leukocytes decrease, platelets decrease, lymphocytes decrease, neutrophils decrease, hemoglobin decrease and creatinine increase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Oncoceptives Inc at 1-866-522-8894 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PEPAXTO is indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) [see *Clinical Studies (14)*].

Limitations of Use

PEPAXTO is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials [see *Warnings and Precautions (5.5)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of PEPAXTO is 40 mg administered intravenously over 30 minutes on Day 1 of each 28-day cycle until disease progression or until unacceptable toxicity. Administer dexamethasone 40 mg orally or intravenously on Days 1, 8, 15 and 22 of each cycle. For patients 75 years of age or older, reduce the dose of dexamethasone to 20 mg. Refer to the prescribing information for dexamethasone for additional dosing information [see *Clinical Studies (14)*].

2.2 Recommended Premedication and Concomitant Medications

Consider providing a serotonin-3 (5-HT₃) receptor antagonist or other antiemetics prior to and during the treatment with PEPAXTO.

2.3 Dosage Modifications for Adverse Reactions

Withhold PEPAXTO if the neutrophil count is less than $1 \times 10^9/L$ or the platelet count is less than $50 \times 10^9/L$.

The recommended dose reductions and dosage modifications for adverse reactions for PEPAXTO are presented in Table 1 and Table 2, respectively.

Table 1: Recommended Dose Reductions for Adverse Reactions of PEPAXTO

Dose Reduction	Dosage*
First	30 mg
Second	20 mg
Subsequent	Permanently discontinue PEPAXTO in patients who are unable to tolerate 20 mg.

* Administered intravenously on Day 1 of each 28-day cycle. For dosage modifications, see Table 2.

Table 2: Recommended Dosage Modifications for Adverse Reactions of PEPAXTO

Adverse Reaction	Severity	Dosage Modification
Myelosuppression [see <i>Warnings and Precautions (5.1, 5.2)</i>]	Platelet count less than $50 \times 10^9/L$ on an intended PEPAXTO dosing day	<ul style="list-style-type: none">Withhold PEPAXTO and monitor platelet count weekly until platelet count is $50 \times 10^9/L$ or greater.Resume PEPAXTO<ul style="list-style-type: none">at same dose if delay is 2 weeks or less.at 1 dose level lower if delay is more than 2 weeks.
	Absolute neutrophil count less than $1 \times 10^9/L$ on an intended PEPAXTO dosing day	<ul style="list-style-type: none">Withhold PEPAXTO and monitor neutrophil count weekly until neutrophil count is $1 \times 10^9/L$ or greater.Resume PEPAXTO<ul style="list-style-type: none">at same dose if delay is 2 weeks or less.at 1 dose level lower if delay is more than 2 weeks.

Adverse Reaction	Severity	Dosage Modification
	Grade 4 hematological adverse reaction on an intended PEPAXTO dosing day in 2 consecutive cycles	<ul style="list-style-type: none"> Resume PEPAXTO at 1 dose level lower.
Non-Hematologic Adverse Reaction [see Adverse Reactions (6.1)]	Grade 2	<ul style="list-style-type: none"> Consider withholding PEPAXTO until resolved to at least Grade 1 or baseline. Consider resuming PEPAXTO at 1 dose level lower.
	Grade 3 or 4	<ul style="list-style-type: none"> Withhold PEPAXTO until resolved to at least Grade 1 or baseline. Resume PEPAXTO at 1 dose level lower as clinically appropriate.

2.4 Preparation and Administration

PEPAXTO is a hazardous drug. Follow applicable special handling and disposal procedures.¹

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

Reconstitute and dilute PEPAXTO prior to infusion.

Additional agents required for preparation:

- 5% Dextrose Injection, USP (room temperature)
- 250 mL bag of **cold (2°C to 8°C / 36°F to 46°F)** 0.9% Sodium Chloride Injection, USP (refrigerate for at least 4 hours)

Preparation Steps:

Read the complete instructions prior to starting preparation.

Steps 3 to 5 must be completed within 30 minutes.

Reconstitution and dilution steps
<p>Step 1</p> <p>Determine the dose, the total volume of reconstituted PEPAXTO solution required, and the number of PEPAXTO vials needed. More than one vial may be needed for a full dose. Place PEPAXTO vial(s) at room temperature for at least 30 minutes.</p>
<p>Step 2</p> <p>Shake the vial(s) vigorously or vortex to disintegrate the lyophilized PEPAXTO powder cake into a loose powder.</p>
<p>Step 3 to 5 must be completed within 30 minutes</p> <p>Step 3</p> <p>Aseptically reconstitute each vial with 40 mL of 5% Dextrose Injection, USP to obtain a final concentration of 0.5 mg/mL. Ensure the 5% Dextrose Injection, USP is room temperature (20°C to 25°C / 68°F to 77°F). Shake the vial(s) vigorously until solution is clear.</p> <p>Let the vial(s) stand to allow air bubbles to dissipate to confirm a clear solution.</p>
<p>Step 4</p> <p>Withdraw 80 mL from a refrigerated (2°C to 8°C / 36°F to 46°F) 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP. Discard the withdrawn 80 mL.</p>
<p>Step 5</p> <p>Withdraw the required volume of reconstituted solution from the PEPAXTO vial(s) and transfer into an intravenous bag containing 0.9% Sodium Chloride Injection, USP to obtain a final concentration of 0.1 mg/mL to 0.16 mg/mL. Discard any unused portion left in the vial(s).</p> <p>Gently invert the bag to mix the solution. Do not shake. Check that the PEPAXTO solution is clear and colorless to pale yellow. Do not use if solution discoloration or particles are observed.</p>

Storage timelines:

PEPAXTO degrades in solution, especially at room temperature, and the storage timelines for diluted solution should not be exceeded:

For immediate administration:

Infusion of the diluted PEPAXTO solution must begin **within 60 minutes** of start of reconstitution (step 3).

For delayed administration:

If not used for immediate administration, the diluted PEPAXTO solution should be placed in a refrigerator (2°C to 8°C / 36°F to 46°F) within 30 minutes after initial reconstitution (step 3) and store for **up to 6 hours**.

Administration:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

Administration steps**Step 6**

Administer PEPAXTO as a 30-minute intravenous infusion via a central venous access device, for example mediport, PICC or tunneled central venous catheter. If the infusion bag has been stored in a refrigerator, allow to reach to room temperature (20°C to 25°C / 68°F to 77°F). Start infusion within 30 minutes of removing the diluted PEPAXTO solution from the refrigerator.

Step 7

Administer PEPAXTO as an intravenous infusion via a central catheter over 30 minutes.

Step 8

Upon completion of PEPAXTO infusion, flush the central catheter per individual institutional guidelines.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 20 mg melphalan flufenamide as a sterile lyophilized white to off-white powder in a single-dose vial for reconstitution and further dilution.

4 CONTRAINDICATIONS

PEPAXTO is contraindicated in patients with a history of serious hypersensitivity reaction to melphalan flufenamide or melphalan [see *Adverse Reactions* (6.1)].

5 WARNINGS AND PRECAUTIONS**5.1 Thrombocytopenia**

Thrombocytopenia was reported in 99% of 157 patients who received PEPAXTO with dexamethasone. Grade 3 thrombocytopenia was reported in 26% and Grade 4 thrombocytopenia was reported in 54% of patients [see *Adverse Reactions* (6.1)]. Thrombocytopenia may lead to hemorrhage. Any Grade hemorrhage was reported in 28% of 157 patients. Grade 3 hemorrhage was reported in 3.2% and Grade 4 hemorrhage was reported in <1% of patients [see *Adverse Reactions* (6.1)].

Grade 3 or 4 thrombocytopenia occurred in 43% of patients during the first cycle, with a median time to onset of 15 days from the first dose.

Monitor platelets at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment with PEPAXTO. Do not administer PEPAXTO if the platelet count is less than 50 x 10⁹/L. Withhold PEPAXTO until platelet count 50 x 10⁹/L or greater and resume at same or reduced dose based on duration of interruption. Adjust dose and/or dose schedule based on signs and symptoms of bleeding [see *Dosage and Administration* (2.3)].

5.2 Neutropenia

Neutropenia was reported in 95% of 157 patients who received PEPAXTO with dexamethasone. 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 [see *Adverse Reactions (6.1)*]. Neutropenia may lead to infection.

Grade 3 or 4 neutropenia occurred in 50% during the first cycle, with a median time to onset of 15 days from the first dose.

Monitor neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment with PEPAXTO. Do not administer PEPAXTO if absolute neutrophil count less than $1 \times 10^9/L$. Withhold PEPAXTO until absolute neutrophil count is $1 \times 10^9/L$ or greater and resume at same or reduced dose based on duration of interruption [see *Dosage and Administration (2.3)*]. Consider leukocyte growth factor as clinically appropriate.

5.3 Anemia

Anemia was reported in 84% of 157 patients who received PEPAXTO with dexamethasone. Grade 3 anemia was reported in 50% of 157 patients [see *Adverse Reactions (6.1)*].

Monitor red blood cell counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment with PEPAXTO. Treat anemia as clinically indicated and as per standard guidelines. Dosage modification and dose delay of PEPAXTO may be required to allow for recovery of red blood cells.

5.4 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.

5.5 Increased Risk of Mortality with PEPAXTO at Dosages Higher than the Recommended Dosage

A nonclinical safety study in dogs with melphalan flufenamide at dosages exceeding the recommended dose for relapsed or refractory multiple myeloma was associated with mortality [see *Nonclinical Toxicology (13.2)*]. There is limited clinical experience of PEPAXTO at dosages higher than recommended. The safety and efficacy of PEPAXTO has not been established for use as a conditioning regimen in patients receiving transplant.

5.6 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.

5.7 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 [see *Use In Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Thrombocytopenia [see *Warnings and Precautions (5.1)*].
- Neutropenia [see *Warnings and Precautions (5.2)*].
- Anemia [see *Warnings and Precautions (5.3)*].
- Infections [see *Warnings and Precautions (5.4)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Relapsed Refractory Multiple Myeloma (RRMM)

The safety of PEPAXTO was evaluated in HORIZON [see *Clinical Studies (14)*]. Patients received PEPAXTO 40 mg intravenously on Day 1 of each 28-day cycle, in combination with dexamethasone 40 mg orally (or 20 mg for patients 75 years and older) on Days 1, 8, 15 and 22 of each cycle (N=157). Patients were enrolled if they had absolute neutrophil count of $1 \times 10^9/L$ or higher and platelet count of $75 \times 10^9/L$ or greater. Among patients who received PEPAXTO, 29% were exposed for 6 months or longer and 6% were exposed for greater than one year.

Serious adverse reactions occurred in 49% of patients who received PEPAXTO. Serious adverse reactions in >3% of patients included pneumonia (10%), respiratory tract infection (6%), thrombocytopenia (5%), febrile neutropenia (5%) and sepsis (3.2%). Fatal adverse reactions occurred in 10 patients (6%) who received PEPAXTO, where general physical health deterioration (1.9%) and respiratory failure (1.3%) represented more than 1%.

Permanent discontinuation of PEPAXTO due to an adverse reaction occurred in 22% of patients. Adverse reactions which resulted in permanent discontinuation of PEPAXTO in >3% of patients included thrombocytopenia (11%).

Dosage interruptions of PEPAXTO due to an adverse reaction occurred in 62% of patients. The adverse reactions which resulted in dosage interruption of PEPAXTO in >3% of patients included thrombocytopenia (43%), neutropenia (29%), anemia (10%), respiratory tract infection (7%), leukopenia (6%) and pyrexia (4.5%).

Dose reductions of PEPAXTO due to an adverse reaction occurred in 27% of patients. Adverse reactions which resulted in dose reductions of PEPAXTO in >3% patients included thrombocytopenia (22%) and neutropenia (6%).

The most common adverse reactions ($\geq 20\%$) were fatigue, nausea, diarrhea, pyrexia and respiratory tract infection. The most common laboratory abnormalities ($\geq 50\%$) were leukocytes decreased, platelets decreased, lymphocytes decreased, neutrophils decreased, hemoglobin decreased and creatinine increased.

Table 3 summarizes the adverse reactions in HORIZON.

Table 3: Adverse reactions ($\geq 10\%$) in Patients with RRMM Who Received PEPAXTO with Dexamethasone in HORIZON

Adverse Reaction	PEPAXTO with Dexamethasone (N=157)	
	All Grades (%)	Grade 3 or 4 (%)
<i>General disorders and administration site disorders</i>		
Fatigue ¹	55	6
Pyrexia ²	24	1.9
Edema peripheral ²	14	1.3
<i>Gastrointestinal disorders</i>		
Nausea ²	32	0.6
Diarrhea	27	0
Constipation ²	15	0.6
Vomiting	13	0
<i>Infections</i>		
Respiratory tract infection ^{2,3}	24	5
Pneumonia ⁴	13	11

Adverse Reaction	PEPAXTO with Dexamethasone (N=157)	
	All Grades (%)	Grade 3 or 4 (%)
<i>Respiratory, thoracic and mediastinal disorders</i>		
Cough ²	17	0
Dyspnea ²	11	1.3
Dyspnea exertional	10	0
<i>Metabolism and nutrition disorders</i>		
Decreased appetite ²	14	0.6
Hypokalemia ²	14	1.3
Hypocalcemia ²	10	0.6
<i>Nervous system disorders</i>		
Headache	13	0
Dizziness	11	0
<i>Musculoskeletal and connective tissue disorders</i>		
Bone pain ²	13	1.9
Pain in extremity ²	13	1.9
Back pain ²	12	0.6
Arthralgia	10	0
<i>Psychiatric disorders</i>		
Insomnia ²	11	0.6

¹ Fatigue includes fatigue and asthenia

² No Grade 4 adverse reactions occurred

³ Respiratory tract infection includes upper respiratory tract infection, lower respiratory tract infection, respiratory tract infection and respiratory tract infection viral

⁴ Pneumonia includes pneumonia, pneumocystis jirovecii pneumonia and pneumonia viral

Clinically relevant adverse reactions in <10% of patients who received PEPAXTO in combination with dexamethasone (N=157) included:

Allergic conditions: hypersensitivity reaction (7%)

Blood and lymphatic system disorders: febrile neutropenia (6%)

Infections: sepsis (3.8%)

Hemorrhages: Grade 3 or 4 hemorrhages (3.8%)

Table 4 summarizes the laboratory abnormalities in HORIZON.

Table 4: Laboratory Abnormalities (≥50%) That Worsened from Baseline in Patients in HORIZON

Laboratory Abnormality	PEPAXTO with Dexamethasone ¹	
	All Grades ² (%)	Grade 3- 4 ³ (%)
Leukocytes decrease	99	88
Platelets decrease	99	80
Lymphocytes decrease	97	95
Neutrophils decrease	95	82
Hemoglobin decrease	84	50
Creatinine increase	68	1 ⁴

¹ Denominators for percentages are the number of patients with assessments at baseline and post-baseline (N=157 for all abnormalities)

² Patients with any worsening grade

³ Patients with worsening to Grade 3 or 4, respectively

⁴ No Grade 4 laboratory abnormality occurred

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action [see *Clinical Pharmacology (12.1)*], PEPAXTO can cause fetal harm when administered to a pregnant woman. There are no available data on PEPAXTO use in pregnant women to evaluate for a drug-associated risk. PEPAXTO is a genotoxic drug [see *Nonclinical Toxicology (13.1)*]. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Animal reproductive or developmental toxicity studies were not conducted with PEPAXTO. Melphalan flufenamide is genotoxic and was toxic to actively dividing cells in animal studies and thus it has the potential to cause teratogenicity and embryo-fetal lethality.

8.2 Lactation

Risk Summary

There is no data on the presence of melphalan flufenamide or its metabolites in human breast milk, or the effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with PEPAXTO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

PEPAXTO can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating PEPAXTO.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with PEPAXTO and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with PEPAXTO and for 3 months after the last dose [see *Nonclinical Toxicology (13.1)*].

Infertility

Females

PEPAXTO can cause amenorrhea in premenopausal women and result in infertility.

Males

Based on findings of melphalan flufenamide in animals, PEPAXTO may impair male fertility [see *Nonclinical Toxicology (13.1)*]. Alkylating drugs, such as PEPAXTO, can also cause irreversible testicular suppression in patients.

8.4 Pediatric Use

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

8.5 Geriatric Use

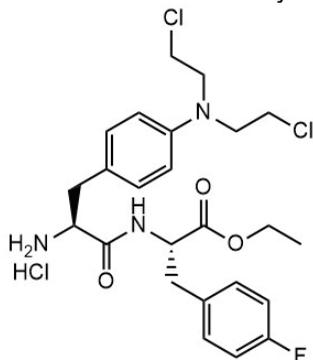
Of the 157 patients with RRMM who received PEPAXTO, 50% were 65 years and older, while 16% were 75 years and older. No overall differences in safety were observed between these patients and younger patients. Clinical studies of PEPAXTO in patients with RRMM did not include sufficient numbers of patients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

8.6 Renal Impairment

No dose adjustment of PEPAXTO is recommended in patients with creatinine clearance (CL_{cr}) 45 to 89 mL/min calculated using Cockcroft-Gault equation [see *Clinical Pharmacology* (12.3)]. PEPAXTO has not been studied in patients with CL_{cr} 15 to 44 mL/min.

11 DESCRIPTION

Melphalan flufenamide is an alkylating drug. The chemical name is Ethyl (2*S*)-2-[[[(2*S*)-2-amino-3-[4-[bis(2-chloroethyl)amino]phenyl]propanoyl]amino]-3-(4-fluorophenyl)propanoate hydrochloride and the molecular weight is 498.4 as free base and 534.9 as the hydrochloride salt. The structural formula is:



Melphalan flufenamide hydrochloride is soluble in most organic solvents, while sparsely soluble in aqueous solutions. The pK_a value is 7.13.

PEPAXTO for injection is supplied as a sterile, white to off-white lyophilized powder in a single-dose vial for intravenous use. Each vial contains 20 mg melphalan flufenamide (equivalent to 21.48 mg melphalan flufenamide hydrochloride) and 1,000 mg sucrose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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, cross-linking 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.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of PEPAXTO have not been fully characterized.

Cardiac Electrophysiology

The effect of PEPAXTO on QT interval has not been fully characterized.

12.3 Pharmacokinetics

Melphalan flufenamide peak plasma concentrations were reached during the 30-minute infusion. Peak plasma concentrations of the active metabolite melphalan were reached 4 to 15 minutes after the end of infusion of PEPAXTO 40 mg. Following PEPAXTO 40 mg, the mean (CV%) C_{max} was 432 ng/mL (30%) and AUC_{0-∞} was 3,143 µg/mL·hr (28%) for melphalan after a single dose. The mean (CV%) C_{max} was 419 ng/mL (33%) and AUC_{0-∞} was 2,933 µg/mL·hr (29%) for melphalan at steady-state.

Distribution

In vivo the disappearance of melphalan flufenamide from plasma is rapid and is attributed to distribution to peripheral tissues with no late redistribution back to plasma.

The mean (CV%) volume of distribution was 35 L (71%) for melphalan flufenamide and 76 L (32%) for melphalan after a single dose.

Elimination

After the end of infusion of PEPAXTO 40 mg, the mean (CV%) elimination half-life of melphalan flufenamide is 2.1 minutes (34%). The mean (CV%) elimination half-life of melphalan is 70 minutes (21%). The mean (CV%) clearance of melphalan flufenamide and melphalan is 692 L/hr (49%) and 23 L/hr (23%), respectively, at the recommended dosage of PEPAXTO 40 mg.

Metabolism

Melphalan flufenamide is metabolized in tissues to desethyl-melphalan flufenamide and melphalan. Melphalan is metabolized primarily by spontaneous hydrolysis to monohydroxy-melphalan and dihydroxy-melphalan.

Specific Populations

Higher melphalan exposures were observed in patients with lower body surface area. No clinically meaningful differences in the PK of melphalan were observed based on age (35 to 85 years old), renal impairment (CLcr 45 to 89 mL/min) and mild hepatic impairment (total bilirubin \leq ULN and AST $>$ ULN, or total bilirubin 1 to 1.5 \times ULN and any AST).

The effect of sex, race/ethnicity, moderate to severe hepatic impairment (total bilirubin $>$ 1.5 \times ULN and any AST), and renal impairment (CLcr 15 to 44 mL/min) on melphalan flufenamide and melphalan PK is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with melphalan flufenamide.

PEPAXTO is genotoxic. In studies conducted in vitro, melphalan flufenamide caused irreversible DNA damage. Repeat-dose toxicity studies with melphalan flufenamide in animals showed adverse effects on male reproductive organs. Melphalan flufenamide was administered intravenously to rats at 20, 40, or 55 mg/m², and to dogs at 0.45 or 0.90 mg/kg (9 or 18 mg/m²) every 21 days for two or three doses. Decreased testes weights and depletion of germ cells were observed in both species, and epididymal oligospermia was observed in dogs. Adverse effects on male reproductive organs were observed in dogs at dose levels less than the recommended clinical dose of 40 mg. The reversibility of adverse effects on male reproductive organs was not assessed.

13.2 Animal Toxicology and/or Pharmacology

Dogs were intravenously administered a single dose of melphalan flufenamide (17.5 mg/kg) or an equimolar dose of melphalan; these dose levels were representative of dosages needed for myeloablation. Increased mortality was observed in dogs administered melphalan flufenamide despite similar melphalan exposure in animals administered melphalan flufenamide or melphalan.

14 CLINICAL STUDIES

The efficacy of PEPAXTO in combination with dexamethasone was evaluated in HORIZON [NCT02963493], a multicenter, single-arm trial. Eligible patients were required to have relapsed or refractory multiple myeloma. Patients received PEPAXTO 40 mg intravenously on Day 1 and dexamethasone 40 mg orally (20 mg for patients \geq 75 years of age) on Day 1, 8, 15 and 22 of each 28-day cycle until disease progression or unacceptable toxicity.

A total of 157 patients accepting a central venous catheter and with estimated creatinine clearance by Cockcroft-Gault formula \geq 45 mL/min were enrolled. Patients with primary refractory disease (i.e. never responded with at least minimal response to any prior treatment) were excluded. Ninety seven patients had received four or more prior lines of therapies and were refractory to at least one proteasome inhibitor, at least one immunomodulatory agent and a CD38-directed monoclonal antibody. The median age was 65 years (range: 35 to 86 years); 58% were male, 87% were White and 6% were Black or African American. Disease characteristics in these 97 patients are summarized in Table 5.

The major efficacy outcome measure was overall response rate (ORR) and Duration of Response (DoR) assessed according to the International Myeloma Working Group (IMWG) Criteria by investigators. Efficacy results in the 97 patients are provided in Table 6. The median time to first response was 2.1 months (range: 1.0 to 6.1 months).

Table 5: Disease Characteristics (HORIZON)

Parameter	PEPAXTO with Dexamethasone (N=97)
Years from diagnosis to start of PEPAXTO, median (range)	6.4 (2.1 to 24.6)
Prior treatment regimens, median (range)	6 (4 to 12)
Documented refractory status, (%)	
Lenalidomide	94
Pomalidomide	92
Bortezomib	74
Carfilzomib	63
Daratumumab	93
Alkylator refractory, (%)	75
Previous stem cell transplant, (%)	70
International Staging System at Baseline, (%)	
I	30
II	32
III	34
Missing/Unknown	4
High-risk cytogenetics ¹ , (%)	33
Extramedullary disease (EMD), (%)	41

¹ del(17p), t(4;14),t(14;16), gain (1q) and t(14;20) at study entry

Table 6: Efficacy Results (HORIZON)

	PEPAXTO with Dexamethasone (N=97)
Overall response rate (ORR), n (%) (95% 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)

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PEPAXTO is a white to off-white lyophilized powder for reconstitution (after reconstitution the solution is clear and colorless to light yellow) supplied in a 50 mL single dose vial containing 20 mg melphalan flufenamide. Each 20 mg vial is packaged in a single carton (NDC 73657-020-01).

The vial stopper is not manufactured with natural rubber latex.

Storage

Store refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light. Retain in original carton until use.

Handling and Disposal

PEPAXTO is a hazardous drug. Follow special handling and disposal procedures.¹ All materials that have been utilized for dilution and administration, including any reconstituted solution made over 30 minutes prior, should be disposed of according to standard procedures for hazardous drugs.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Thrombocytopenia, Neutropenia and Anemia

- Advise patients that PEPAXTO can cause myelosuppression. Advise patients to immediately report signs or symptoms of thrombocytopenia (bleeding and easy bruising), neutropenia (symptoms of infection, such as fever, chills, cough, pain, or burning during urination) and anemia (fatigue and shortness of breath) to their healthcare provider.
- Advise patients that complete blood counts will be monitored at baseline, during treatment, and as clinically indicated [see *Warnings and Precautions* (5.1, 5.2, 5.3)].

Infections

Advise patients that PEPAXTO can cause infections. Instruct patients to immediately report new or worsening signs or symptoms (e.g., chills, fever) of infection to their healthcare provider [see *Warnings and Precautions* (5.4)].

Secondary Malignancies

Advise patients on the risk of second primary malignancies [see *Warnings and Precautions* (5.6)].

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.7) and *Use in Specific Populations* (8.1)].
- Advise females of reproductive potential to use effective contraception during treatment with PEPAXTO and 6 months after the last dose [see *Use in Specific Populations* (8.3)].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with PEPAXTO and for 3 months after the last dose [see *Use in Specific Populations* (8.3)].

Lactation

Advise women not to breastfeed during treatment with PEPAXTO and for 1 week after the last dose [see *Use in Specific Populations* (8.2)].

Manufactured for: Oncopeptides AB (publ), Stockholm, Sweden.

Distributed by: Oncopeptides Inc. 200 Fifth Avenue, Suite #1030 Waltham, MA 02451, USA

PEPAXTO is a registered trademark of Oncopeptides AB (publ)

PATIENT INFORMATION
PEPAXTO (peh-PAX-toe)
(melphalan flufenamide)
for injection, for intravenous use

What is PEPAXTO?

PEPAXTO is a prescription medicine used in combination with the medicine dexamethasone to treat adults with multiple myeloma who did not respond to or stopped responding to at least four prior medicines including at least one proteasome inhibitor, one immunomodulatory agent and one CD38-directed antibody.

PEPAXTO is not for use to prepare for transplant.

It is not known if PEPAXTO is safe and effective in children.

Do not receive PEPAXTO if you have a history of a severe allergic reaction to melphalan flufenamide or melphalan.

Before receiving PEPAXTO, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection
- are pregnant or plan to become pregnant. PEPAXTO may harm your unborn baby.
Females who are able to become pregnant:
 - Your healthcare provider will check to see if you are pregnant before you start treatment with PEPAXTO.
 - You should use an effective method of birth control (contraception) during treatment and for 6 months after the last dose of PEPAXTO.
 - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with PEPAXTO.
- **Males with female partners who are able to become pregnant:**
 - You should use an effective method of birth control (contraception) during treatment and for 3 months after the last dose of PEPAXTO.
 - Talk to your healthcare provider about effective methods of birth control that you can use during this time.
- are breastfeeding or plan to breastfeed. It is not known if PEPAXTO passes into breast milk. Do not breastfeed during treatment with and for 1 week after the last dose of PEPAXTO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive PEPAXTO?

- PEPAXTO is given to you by your healthcare provider into your vein through intravenous (IV) infusion over 30 minutes.
- PEPAXTO is usually given 1 time every 28 days.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests before and during your treatment with PEPAXTO to check for side effects.
- Your healthcare provider may prescribe medicines to help prevent nausea before your infusion and during treatment with PEPAXTO.

What are the possible side effects of PEPAXTO?

PEPAXTO may cause serious side effects, including:

- **Low blood cell counts** are common with PEPAXTO and can be serious. Your healthcare provider will do blood tests as needed to check your blood cell counts during your treatment with PEPAXTO.
 - **Low platelet counts:** Tell your healthcare provider right away if you have a bleeding or bruising under the skin.
 - **Low red blood cell counts:** Tell your healthcare provider if you are feeling weak, tired or you get tired easily, you look pale, or if you feel short of breath.
 - **Low white blood cell counts:** A low white blood cell count increases the risk of infections.
- **Infections.** PEPAXTO can cause infections that have led to death. **Tell your healthcare provider right away if you develop new or worsening signs or symptoms of infection such as fever, chills, cough, pain, or burning during urination during treatment with PEPAXTO.**

- **Secondary cancers.** New cancers such as myelodysplastic syndromes or acute leukemia have happened in people with multiple myeloma who have received PEPAXTO. Your healthcare provider will monitor you for new cancers.

Your healthcare provider may change your dose of PEPAXTO, stop your treatment for a period of time, or completely stop your treatment if you have certain side effects.

PEPAXTO may cause fertility problems in males and females, which may affect your ability to have children. Talk with your healthcare provider if you have concerns about fertility.

The most common side effects of PEPAXTO include, low blood cell counts, fatigue, nausea, diarrhea, fever, and cold-like symptoms (respiratory tract infection).

These are not all of the possible side effects of PEPAXTO.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

General information about the safe and effective use of PEPAXTO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about PEPAXTO that is written for health professionals.

What are the ingredients in PEPAXTO?

Active ingredient: melphalan flufenamide

Inactive ingredient: sucrose

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For more information, go to www.PEPAXTO.com or call 1-866-522-8894.