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Section:	Prescription Drugs	**Effective Date:**	July 1, 2024
Subsection:	Antineoplastic Agents	**Original Policy Date:**	March 26, 2021
Subject:	Pepaxto	**Page:**	1 of 5

Last Review Date: June 13, 2024

Pepaxto

Description

Pepaxto (melphalan flufenamide)

Background
Pepaxto (melphalan flufenamide) is a peptide conjugated alkylating drug. Due to its lipophilicity, it 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 Pepaxto. Pepaxto inhibits proliferation and induces apoptosis of hematopoietic and solid tumor cells. It also shows synergistic cytotoxicity with dexamethasone in melphalan resistant and non-resistant multiple myeloma cell lines (1).

Regulatory Status
FDA-approved 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 (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).

Pepaxto may cause thrombocytopenia, neutropenia, and anemia. Platelets, neutrophil counts, and red blood cell counts should be monitored at baseline, during treatment, and as clinically indicated. Pepaxto should not be administered if the platelet count is less than 50 x 10^9/L or if the absolute neutrophil count is less than 1 x 10^9/L (1).

Secondary malignancies such as myelodysplastic syndromes or acute leukemia have occurred in patients with multiple myeloma who have received Pepaxto. Patients should be monitored long-term for the development of secondary malignancies (1).

Pepaxto can cause fetal harm when administered to a pregnant woman. Pregnant woman should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with Pepaxto and for 6 months after the last dose. Males with female partners of reproductive potential should be advised to use effective contraception during treatment with Pepaxto and for 3 months after the last dose (1).

The safety and effectiveness of Pepaxto in pediatric patients less than 18 years of age have not been established (1).

Related policies
Evomela

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Pepaxto may be considered **medically necessary** if the conditions indicated below are met.

Pepaxto may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Relapsed or refractory multiple myeloma (MM)
    a. Used in combination with dexamethasone
    b. Patient has received at least **FOUR** prior lines of therapy for multiple myeloma

c. Disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody

AND ALL of the following:

1. Prescriber agrees to monitor platelets, neutrophil counts, and red blood cell counts
2. Prescriber agrees to withhold Pepaxto in the following scenarios:
    a. Platelet count is less than 50 x 10^9/L
    b. Absolute neutrophil count is less than 1 x 10^9/L
3. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Pepaxto and for 6 months after the last dose
4. Males with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Pepaxto and for 3 months after the last dose

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Relapsed or refractory multiple myeloma (MM)
    a. Used in combination with dexamethasone

AND ALL of the following:

1. **NO** disease progression or unacceptable toxicity
2. Prescriber agrees to monitor platelets, neutrophil counts, and red blood cell counts
3. Prescriber agrees to withhold Pepaxto in the following scenarios:
    a. Platelet count is less than 50 x 10^9/L
    b. Absolute neutrophil count is less than 1 x 10^9/L
4. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Pepaxto and for 6 months after the last dose

5. Males with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Pepaxto and for 3 months after the last dose

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 6 vials per 84 days

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Pepaxto (melphalan flufenamide) is a peptide conjugated alkylating drug. Due to its lipophilicity, it 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 Pepaxto. Pepaxto inhibits proliferation and induces apoptosis of hematopoietic and solid tumor cells. It also shows synergistic cytotoxicity with dexamethasone in melphalan resistant and non-resistant multiple myeloma cell lines. The safety and effectiveness of Pepaxto in pediatric patients less than 18 years of age have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Pepaxto while maintaining optimal therapeutic outcomes.

References

1. Pepaxto [package insert]. Waltham, MA: Oncopeptides Inc.; February 2021.
2. NCCN Clinical Practice Guidelines in Oncology® Multiple Myeloma (Version 3.2024). National Comprehensive Cancer Network, Inc. March 2024. Accessed on April 23, 2024.

Policy History

Date	Action
March 2021	Addition to PA
June 2021	Annual review and reference update
June 2022	Annual review and reference update
March 2023	Annual review and reference update
June 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 13, 2024 and is effective on July 1, 2024.