Clinical Policy: Melphalan Flufenamide (Pepaxto)

Reference Number: CP.PHAR.535
Effective Date: 06.01.21
Last Review Date: 05.24
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Melphalan flufenamide (Pepaxto®) is an alkylating drug.

FDA Approved Indication(s)*

Pepaxto is indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 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).

Limitation(s) of use: Pepaxto is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials.

***Oncopeptides, the manufacturer of Pepaxto, voluntarily withdrew Pepaxto after data from the confirmatory Phase 3 OCEAN study revealed Pepaxto did not meet the requirements of the FDA Accelerated Approval regulation. The FDA withdrew its approval for the product (*see Appendix D*).**

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Pepaxto is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Multiple Myeloma (must meet all)**:**

1. Provider attestation of acknowledgement of FDA's request for withdrawal of product due to reduced overall survival and failure to demonstrate superior progression-free survival (PFS) compared to Pomalyst® in combination with dexamethasone;
2. Diagnosis of multiple myeloma;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age ≥ 18 years;
5. Pepaxto is prescribed in combination with dexamethasone;

6. Member has received ≥ 4 prior lines of therapy (*see Appendix B for examples*) that include all of the following (a, b, and c):
   a. One proteasome inhibitor (e.g., bortezomib, Kyprolis®, Ninlaro®);
   b. One immunomodulatory agent (e.g., lenalidomide, Pomalyst®, Thalomid®);
   c. One anti-CD38 antibody (e.g., Darzalex®/Darzalex Faspro®, Sarclisa®);
   **Prior authorization may be required*
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 40 mg every 4 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Multiple Myeloma (must meet all)**:**

1. Provider attestation of acknowledgement of FDA's request for withdrawal of product due to reduced overall survival and failure to demonstrate superior PFS compared to Pomalyst in combination with dexamethasone;
2. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Pepaxto for a covered indication and has received this medication for at least 30 days;
3. Member is responding positively to therapy;
4. Pepaxto is prescribed in combination with dexamethasone;
5. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 40 mg every 4 weeks;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CI: confidence interval
FDA: Food and Drug Administration
HR: hazard ratio
PFS: progression free survival

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
bortezomib/lenalidomide/dexamethasone	Varies	Varies
bortezomib/cyclophosphamide/dexamethasone	Varies	Varies
bortezomib/doxorubicin (or liposomal doxorubicin)/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib)/lenalidomide/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib)/cyclophosphamide/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib – weekly or twice weekly)/ dexamethasone	Varies	Varies
Ninlaro® (ixazomib)/lenalidomide/dexamethasone	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Ninlaro® (ixazomib)/dexamethasone	Varies	Varies
Ninlaro® (ixazomib)/pomalidomide/dexamethasone	Varies	Varies
bortezomib/dexamethasone	Varies	Varies
bortezomib/Thalomid® (thalidomide)/dexamethasone	Varies	Varies
cyclophosphamide/lenalidomide/ dexamethasone	Varies	Varies
lenalidomide/dexamethasone	Varies	Varies
VTD-PACE (dexamethasone/Thalomid® (thalidomide)/ cisplatin/doxorubicin/cyclophosphamide/etoposide/ bortezomib)	Varies	Varies
lenalidomide/low-dose dexamethasone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/bortezomib/ melphan/prednisone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/ bortezomib/dexamethasone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/Revlimid® (lenalidomide)/dexamethasone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/pomalidomide/ dexamethasone	Varies	Varies
Empliciti® (elotuzumab)/lenalidomide/ dexamethasone	Varies	Varies
Empliciti® (elotuzumab)/bortezomib/dexamethasone	Varies	Varies
Empliciti® (elotuzumab)/pomalidomide/dexamethasone	Varies	Varies
bendamustine/bortezomib/dexamethasone	Varies	Varies
bendamustine/lenalidomide/dexamethasone	Varies	Varies
panobinostat/bortezomib/dexamethasone	Varies	Varies
panobinostat/Kyprolis® (carfilzomib)	Varies	Varies
panobinostat/lenalidomide/dexamethasone	Varies	Varies
pomalidomide/cyclophosphamide/dexamethasone	Varies	Varies
pomalidomide/dexamethasone	Varies	Varies
pomalidomide/bortezomib/dexamethasone	Varies	Varies
pomalidomide/Kyprolis® (carfilzomib)/dexamethasone	Varies	Varies
Sarclisa® (isatuximab-irfc)/pomalidomide/ dexamethasone	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): history of serious hypersensitivity reaction to melphalan flufenamide or melphalan

- Boxed warning(s): none reported

Appendix D: Withdrawal from Market

- Oncopeptides, the manufacturer of Pepaxto, voluntarily withdrew Pepaxto after data from the confirmatory Phase 3 OCEAN study revealed Pepaxto did not meet the requirements of the FDA Accelerated Approval regulation. The FDA Oncologic Drugs Advisory Committee review of the OCEAN study concluded the following:
  - The median overall survival was 19.7 months in the Pepaxto arm, compared to 25 months in the Pomalyst arm, HR 1.104 (95% CI 0.846, 1.441), indicating a safety concern.
  - The PFS results showed no statistical difference, with a HR 0.82 (95% CI 0.654, 1.027), indicating a lack of confirmed clinical benefit.
- Previously at the FDA's request, Oncopeptides stopped marketing Pepaxto in the US on October 22, 2021, and Pepaxto is currently not commercially available in the US but was available via the Individual Patient Expanded Access Investigational Drug Application (IND) process if deemed appropriate by the treating physician. At this same time Oncopeptides indicated that they planned to voluntarily withdraw Pepaxto, but later rescinded the withdrawal request and submitted additional analyses of the OCEAN study. This led to the September 2022 Oncologic Drugs Advisory Committee review that voted 14 to 2 that Pepaxto's benefit/risk profile was unfavorable.
- The Multiple Myeloma Research Foundation suggests those currently on Pepaxto therapy should contact their treating physician to see if remaining on therapy is appropriate.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Multiple myeloma	40 mg IV infusion on Day 1 of each 28-day treatment cycle, in combination with dexamethasone	40 mg/dose

VI. Product Availability

Lyophilized powder in a single-dose vial for reconstitution and dilution for injection: 20 mg

VII. References

1. Pepaxto Prescribing Information. Waltham, MA: Oncopeptides Inc.; February 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214383s000lbl.pdf. Accessed February 2, 2024.
2. National Comprehensive Cancer Network. Multiple Myeloma Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed February 2, 2024.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed February 2, 2024.
4. Press release: Oncopeptides provides update on Pepaxto US marketing authorization. December 7, 2022. Available at: https://www.oncopeptides.com/en/media/press-releases/oncopeptides-provides-update-on-pepaxto-us-marketing-authorization. Accessed February 2, 2024.

5. FDA Oncologic Drugs Advisory Committee: FDA Presentations, NDA214383 – Pepaxto. September 23, 2022. Available at: https://www.fda.gov/media/161761/download. Accessed February 2, 2024.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9247	Injection, melphalan flufenamide, 1 mg
J9248	Injection, melphalan (hepzato), 1 mg
J9249	Injection, melphalan (apotex), 1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
RT4: Policy created.	03.10.21	05.21
2Q 2022 annual review: updated HCPCS code; for consistency per label added requirement from initial authorization to continuation of therapy requiring that Pepaxto is prescribed in combination with dexamethasone; references reviewed and updated.	02.02.22	05.22
Template changes applied to other diagnoses/indications.	10.05.22	
RT4: added disclaimer about FDA and manufacturer withdrawal; added requirement for prescriber attestation to all criteria sets; added Appendix D.	12.14.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	02.15.23	05.23
Added HCPCS codes [J9248, J9249]	02.20.24	
2Q 2024 annual review: no significant changes; references reviewed and updated.	02.02.24	05.24

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.