Clinical Policy: Melphalan flufenamide (Pepaxto)

Reference Number: PA.CP.PHAR.535
Effective Date: 07/2021
Last Review Date: 01/2023

Coding Implications
Revision Log

Description
Melphalan flufenamide (Pepaxto®) is an alkylating drug.

FDA Approved Indication(s)
Pepaxto is indicated 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).

Limitations 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 PA Health & Wellness® 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., Revlimid®, 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*).

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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*).

Approval duration: 12 months

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 – PA.CP.PMN.53

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/Revlimid® (lenalidomide)/dexamethasone	Varies	Varies
bortezomib/cyclophosphamide/dexamethasone	Varies	Varies
bortezomib/doxorubicin (or liposomal doxorubicin)/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib) Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib)/cyclophosphamide/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib – weekly or twice weekly)/ dexamethasone	Varies	Varies
Ninlaro® (ixazomib)/Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
Ninlaro® (ixazomib)/dexamethasone	Varies	Varies
Ninlaro® (ixazomib)/pomalidomide/dexamethasone	Varies	Varies
bortezomib/dexamethasone	Varies	Varies
bortezomib/Thalomid® (thalidomide)/dexamethasone	Varies	Varies
cyclophosphamide/Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
Revlimid® (lenalidomide)/dexamethasone	Varies	Varies
VTD-PACE (dexamethasone/Thalomid® (thalidomide)/ cisplatin/doxorubicin/cyclophosphamide/etoposide/ bortezomib)	Varies	Varies
Revlimid® (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)/Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
Empliciti® (elotuzumab)/bortezomib/dexamethasone	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Empliciti® (elotuzumab)/pomalidomide/dexamethasone	Varies	Varies
bendamustine/bortezomib/dexamethasone	Varies	Varies
bendamustine/Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
panobinostat/bortezomib/dexamethasone	Varies	Varies
panobinostat/Kyprolis® (carfilzomib)	Varies	Varies
panobinostat/Revlimid® (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, 2022.
2. National Comprehensive Cancer Network. Multiple Myeloma Version 4.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed February 2, 2022.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed February 2, 2022.
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 December 15, 2022.
5. FDA Oncologic Drugs Advisory Committee: FDA Presentations, NDA214383 – Pepaxto. September 23, 2022. Available at: https://www.fda.gov/media/161761/download. Accessed December 15, 2022.

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	07/2021	
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.	04/2022	
RT4: added disclaimer about FDA and manufacturer withdrawal; added requirement for prescriber attestation to all criteria sets; added Appendix D.	01/2023	