Pepaxto® (melphalan flufenamide)
(Intravenous)

I. Length of Authorization

Coverage is provided for six months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC unit]:
   - Pepaxto 20 mg single-dose vial: 2 vials every 28 days

B. Max Units (per dose and over time) [HCPCS Unit]:
   - 40 mg (billable units) on Day 1 of each 28-day treatment cycle

III. Initial Approval Criteria

Coverage is provided in the following conditions:

- Patient is at least 18 years or older; AND

Universal Criteria

- Patient does not have a history of serious allergic reactions to melphalan; AND
- Therapy will NOT be used as a conditioning regimen for transplant; AND

Multiple Myeloma (MM) †

- Patient has relapsed, refractory, or progressive disease; AND
- Used in combination with dexamethasone; AND
- Patient received at least four prior lines of therapy and is refractory to a proteasome inhibitor (e.g., bortezomib, carfilzomib, etc.) an immunomodulatory agent (e.g., lenalidomide, pomalidomide, etc.) and a CD38-directed antibody (e.g., daratumumab, isatuximab, etc.); AND
- Provider attests to discussing with patient the possible risks and benefits of therapy with Pepaxto in the context of other treatments and will monitor therapy accordingly

*
*Note: On July 27, 2021, the FDA issued a CDER alert to patients and health care professionals that the pivotal study OCEAN, Study OP-103 evaluating Pepaxto (melphalan flufenamide) with dexamethasone to treat patients with multiple myeloma showed an increased risk of death. As a result, the FDA encouraged health care professionals to review patients’ progress on Pepaxto and discuss the risks of continued administration with each patient in the context of other treatments. Also, patients currently receiving Pepaxto were advised to discuss with their health care professional the risks and benefits of receiving Pepaxto.

† FDA indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

IV. Renewal Criteria

Coverage can be renewed based on the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; AND
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include severe thrombocytopenia, severe neutropenia, severe anemia, clinically significant infections, secondary malignancies, etc.; AND
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; AND
- Provider attests to discussing with the patient the risks and benefits of continued therapy with Pepaxto in the context of other treatments*

*Note: On July 27, 2021, the FDA issued a CDER alert to patients and health care professionals that the pivotal study OCEAN, Study OP-103 evaluating Pepaxto (melphalan flufenamide) with dexamethasone to treat patients with multiple myeloma showed an increased risk of death. As a result, the FDA encouraged health care professionals to review patients’ progress on Pepaxto and discuss the risks of continued administration with each patient in the context of other treatments. Also, patients currently receiving Pepaxto were advised to discuss with their health care professional the risks and benefits of receiving Pepaxto.

V. Dosage/Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Myeloma</td>
<td>The recommended dose of Pepaxto is 40 mg administered as a single intravenous infusion over 30 minutes on day 1 of each 28-day treatment cycle, in combination with dexamethasone, until disease progression or until unacceptable toxicity.</td>
</tr>
</tbody>
</table>
VI. Billing Code/Availability Information

HCPCS:
- J9999 – Not otherwise classified, antineoplastic drug
- C9080 – Injection, melphalan flufenamide hydrochloride, 1 mg; 1 billable unit = 1 mg (hospital outpatient use)

NDC:
- Pepaxto 20 mg lyophilized powder in a single-dose vial for reconstitution: 73657-0020-xx

VII. References
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for melphalan flufenamide. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed May 2021

Appendix 1 – Covered Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>ICD-10 Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C90.00</td>
<td>Multiple myeloma not having achieved remission</td>
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</table>
Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD) and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD): N/A

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Applicable State/US Territory</th>
<th>Contractor</th>
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<tbody>
<tr>
<td>E (1)</td>
<td>CA, HI, NV, AS, GU, CNMI</td>
<td>Noridian Healthcare Solutions, LLC</td>
</tr>
<tr>
<td>F (2 &amp; 3)</td>
<td>AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ</td>
<td>Noridian Healthcare Solutions, LLC</td>
</tr>
<tr>
<td>5</td>
<td>KS, NE, IA, MO</td>
<td>Wisconsin Physicians Service Insurance Corp (WPS)</td>
</tr>
<tr>
<td>6</td>
<td>MN, WI, IL</td>
<td>National Government Services, Inc. (NGS)</td>
</tr>
<tr>
<td>H (4 &amp; 7)</td>
<td>LA, AR, MS, TX, OK, CO, NM</td>
<td>Novitas Solutions, Inc.</td>
</tr>
<tr>
<td>8</td>
<td>MI, IN</td>
<td>Wisconsin Physicians Service Insurance Corp (WPS)</td>
</tr>
<tr>
<td>N (9)</td>
<td>FL, PR, VI</td>
<td>First Coast Service Options, Inc.</td>
</tr>
<tr>
<td>J (10)</td>
<td>TN, GA, AL</td>
<td>Palmetto GBA, LLC</td>
</tr>
<tr>
<td>M (11)</td>
<td>NC, SC, WV, VA (excluding below)</td>
<td>Palmetto GBA, LLC</td>
</tr>
<tr>
<td>L (12)</td>
<td>DE, MD, PA, NJ, DC (includes Arlington &amp; Fairfax counties and the city of Alexandria in VA)</td>
<td>Novitas Solutions, Inc.</td>
</tr>
<tr>
<td>K (13 &amp; 14)</td>
<td>NY, CT, MA, RI, VT, ME, NH</td>
<td>National Government Services, Inc. (NGS)</td>
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<td>15</td>
<td>KY, OH</td>
<td>CGS Administrators, LLC</td>
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