Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Carfilzomib (Kyprolis®)	MP-RX-FP-51-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *carfilzomib (Kyprolis®),* a protease inhibitor, approved by the Food and Drug Administration (FDA) for the treatment of multiple myeloma and Waldenström's macroglobulinemia.

Background Information

The FDA approved indications for Kyprolis include treatment for relapsed or refractory multiple myeloma: in combination with dexamethasone with or without lenalidomide in those who have received one to three lines of therapy, or as a single agent in those who have received one or more lines of therapy. The FDA label includes several warnings for the use of Kyprolis, including cardiac toxicities. In clinical studies, congestive heart failure, pulmonary edema, or decreased ejection fraction (either a new onset or a worsening of previous condition) has led to death due to cardiac arrest within 1 day of administration of carfilzomib. Individuals with New York Heart Association Class III and IV heart failure were ineligible for clinical trials.

The National Comprehensive Cancer Network® (NCCN) provides additional category 2A recommendations for the use of Kyprolis in combination with various agents as primary therapy, maintenance therapy, and therapy for relapsed/refractory disease. NCCN also recommends Kyprolis for Waldenström's macroglobulinemia (also called lymphoplasmacytic lymphoma) a type of non-Hodgkin's lymphoma. It is used in combination with rituximab and dexamethasone for primary treatment as well as treatment for relapsed disease. The NCCN guidelines for systemic light chain amyloidosis additionally recommend carfilzomib in non-cardiac disease and for those with significant neuropathy.

Definitions and Measures

- Line of Therapy:
  - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
  - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
  - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- Multiple myeloma: A type of cancer that begins in plasma cells (white blood cells that produce antibodies).

Policy Name	Policy Number	Scope
Carfilzomib (Kyprolis®)	MP-RX-FP-51-23	☒ MMM MA ☒ MMM Multihealth

- Proteasome inhibitors: A class of drugs used to treat multiple myeloma that work by blocking the action of proteasomes which are cellular complexes that break down proteins. Examples include bortezomib, carfilzomib and ixazomib.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Approved Indications

FDA Approved Indication
1. For the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with: ○ Lenalidomide and dexamethasone; or ○ Dexamethasone; or ○ Daratumumab and dexamethasone; or ○ Daratumumab and hyaluronidase-fihj and dexamethasone; or ○ Isatuximab and dexamethasone.
2. As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

Other Uses

i. N/A

Policy Name	Policy Number	Scope
Carfilzomib (Kyprolis®)	MP-RX-FP-51-23	☒ MMM MA ☒ MMM Multihealth

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9047	Injection, carfilzomib, 1 mg [Kyprolis]

ICD-10	Description
C83.00-C83.09	Small cell B-cell lymphoma [lymphoplasmacytic lymphoma]
C88.0	Waldenström's macroglobulinemia
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Clinical Criteria

Kyprolis® (carfilzomib)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of multiple myeloma; **AND**
ii. Individual does not have New York Heart Association (NYHA) class III or IV heart failure; **AND**
iii. Individual is using for one of the following:
   A. Primary treatment in combination with lenalidomide plus dexamethasone (NCCN 2A); **OR**
   B. Primary treatment in combination with daratumumab, lenalidomide, and dexamethasone (NCCN 2A);

Policy Name	Policy Number	Scope
Carfilzomib (Kyprolis®)	MP-RX-FP-51-23	☒ MMM MA ☒ MMM Multihealth

OR

C. Primary treatment in combination with cyclophosphamide and dexamethasone for individuals with renal insufficiency and/or peripheral neuropathy (NCCN 2A);

OR

D. In combination with lenalidomide as maintenance therapy for high-risk multiple myeloma in transplant candidates (NCCN 2A);

OR

E. Treatment for previously treated relapsed, refractory, or progressive disease with one of the following:

1. In combination with dexamethasone with or without lenalidomide when the individual has received one to three prior lines of therapy; **OR**
2. As a single agent when the individual has received one or more prior lines of therapy; **OR**
3. In combination with pomalidomide and dexamethasone (NCCN 2A); **OR**
4. In combination with daratumumab (or daratumumab and hyaluronidase-fihj) and dexamethasone; **OR**
5. In combination with isatuximab and dexamethasone; **OR**
6. In combination with selinexor and dexamethasone (NCCN 2A); **OR**
7. In combination with cyclophosphamide and dexamethasone (NCCN 2A); **OR**
8. In combination with cyclophosphamide, thalidomide, and dexamethasone (NCCN 2A); **OR**
9. In combination with venetoclax and dexamethasone for patients with t(11;14) (NCCN 2A); **OR**
10. In combination with bendamustine and dexamethasone when the individual has received at least 3 prior therapies (NCCN 2A);

OR

iv. Individual has a diagnosis of Waldenström's macroglobulinemia (NCCN 2A); **AND**

v. Individual does not have New York Heart Association (NYHA) class III or IV heart failure; **AND**

vi. Carfilzomib is used for one of the following:

A. As a primary agent, in combination with rituximab (or rituximab biosimilar) and dexamethasone; **OR**

B. For relapsed disease when the primary therapy of carfilzomib, rituximab (or rituximab biosimilar), and dexamethasone was given and relapse is greater than 12 months after therapy;

OR

vii. Individual has a diagnosis of Systemic Light Chain Amyloidosis (NCCN 2A); **AND**

viii. Individual does not have New York Heart Association (NYHA) class III or IV heart failure; **AND**

ix. Carfilzomib is used as a single agent or in combination with dexamethasone for relapsed or refractory on-cardiac disease; **OR**

x. Carfilzomib is used in combination with dexamethasone as primary therapy for individuals with significant neuropathy.

Policy Name	Policy Number	Scope
Carfilzomib (Kyprolis®)	MP-RX-FP-51-23	☒ MMM MA ☒ MMM Multihealth

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Kyprolis® (carfilzomib) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:

A. A current oncology note (chart notes) documenting the patient's response to treatment showing no progression of disease.

B.Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results (every six months).

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months

ii. Reauthorization Approval Duration: Up to 6 months

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for Kyprolis (carfilzomib) may not be approved when the criteria above (section A: Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Policy Name	Policy Number	Scope
Carfilzomib (Kyprolis®)	MP-RX-FP-51-23	☒ MMM MA ☒ MMM Multihealth

Kyprolis® (carfilzomib)

Indication	Recommended Dosing	Treatment Duration
For the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with: ○ Lenalidomide and dexamethasone; or ○ Dexamethasone; or ○ Daratumumab and dexamethasone; or ○ Daratumumab and hyaluronidase-fihj and dexamethasone; or ○ Isatuximab and dexamethasone.	*** Dose will vary depending on concomitant agents: • 20/70 mg/m2 on days 1, 8, and 15 of each 28-day cycle when Kyprolis is administered in combination with: ○ Dexamethasone (Kd), ○ Daratumumab plus dexamethasone (DKd) ○ Daratumumab and hyaluronidase-fihj plus dexamethasone (DKd)	Until disease progression or unacceptable toxicity
As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.	• Twice Weekly 20/56 mg/m2 administered as monotherapy or in combination with: ○ Dexamethasone (Kd) ○ Daratumumab plus dexamethasone (DKd) ○ Daratumumab and hyaluronidase-fihj plus dexamethasone (DKd) ○ Isatuximab plus dexamethasone (Isa-Kd) • Twice Weekly 20/27 mg/m2 administered as monotherapy or in combination with lenalidomide and dexamethasone (KRd).	
Exceptions		
• For the 20/70 mg/m^2 regimen: The recommended starting dosage of Kyprolis is 20 mg/m^2 on Cycle 1, Day 1.		

Policy Name	Policy Number	Scope
Carfilzomib (Kyprolis®)	MP-RX-FP-51-23	☒ MMM MA ☒ MMM Multihealth

If tolerated, escalate the dose to 70 mg/m^2 on Cycle 1, Day 8. Continue 70 mg/m^2 for subsequent doses.

- For the twice weekly 20/56 mg/m^2 regimen: The recommended starting dosage of Kyprolis is 20 mg/m^2 on Cycle 1, Days 1 and 2 (first week). If tolerated, escalate the dose to 56 mg/m^2 on Cycle 1, Day 8. Continue 56 mg/m^2 for subsequent doses.
- For the twice weekly 20/27 mg/m^2 regimen: The recommended starting dosage of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2 (first week). If tolerated, escalate the dose to 27 mg/m^2 on Day 8 of Cycle 1 and thereafter.
- Dose Calculation:
  - For patients with body surface area (BSA) of 2.2 m^2 or less, Kyprolis dose should be calculated using actual BSA. Dose adjustments do not need to be made for weight changes of 20% or less.
  - For patients with a BSA greater than 2.2 m^2, Kyprolis dose should be calculated using a BSA of 2.2 m^2.

Reference Information

1. Bringhen S, Petrucci MT, Larocca A, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood. 2014; 124(1):63-69.
2. Bringhen S, D'agostino M, De Paoli L, et al. Phase I/II study of weekly carfilzomib, cyclophosphamide, dexamethasone in newly diagnosed transplant-ineligible myeloma. Leukemia 2018; 32: 979-985.
3. Chari A, Martinez-Lopez J, Mateos M, et al. Daratumumab in combination with carfilzomib and dexamethasone in lenalidomide-refractory patients with relapsed multiple myeloma: Subgroup analysis of MMY1001. J Clin Oncol. 2018; 36(15):8002-8002
4. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 24, 2023.
5. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
6. Jakubowiak A, Chari A, Lonial S, et al. Daratumumab in combination with carfilzomib, lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma (MMY1001). J Clin Oncol. 2017; 35(15):8000-8000
7. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
8. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 24, 2023.
   a. Multiple Myeloma. V3.2023. Revised December 8, 2022.
   b. Systemic Light Chain Amyloidosis. V2.2023. Revised November 28, 2022.
   c. Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma. V1.2023. Revised July 6, 2022.

9. Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. Blood. 2015; 126(20):2284-2290.
10. Manwani R, Mahmood S, Sachchithanantham S, et al. Carfilzomib is an effective upfront treatment in AL amyloidosis patients with peripheral and autonomic neuropathy. Br J Haematol. 2019; 187:638-641.
11. Mikhael JR, Reeder CB, Libby EN, et al. A phase I/II trial of cyclophosphamide, carfilzomib, thalidomide and dexamethasone (CYCLONE) in patients with newly diagnosed multiple myeloma: Final Results of MTD expansion cohort. Blood 2013; 122:3179.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 10/12/2024	Wording and formatting updates. Coding reviewed: No changes.	2/24/2025	3/6/2025
Select Review	Updates per NCCN: add combination use with cyclophosphamide regimens, venetioclax, bendamustine, and selinexor; update combination use with pomalidomide; add use as maintenance therapy in multiple myeloma; add primary therapy in systemic light chain amyloidosis; wording and formatting updates. Coding Reviewed: No changes.	8/8/2024	8/15/2024
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

Policy Name	Policy Number	Scope
Carfilzomib (Kyprolis®)	MP-RX-FP-51-23	☒ MMM MA ☒ MMM Multihealth