Clinical Policy: Carfilzomib (Kyprolis)

Reference Number: PA.CP.PHAR.309
Effective Date: 10/2018
Last Review Date: 10/2024

Description
Carfilzomib (Kyprolis®) is a proteasome inhibitor.

FDA Approved Indication(s)
Kyprolis is indicated

- For the treatment of adult patients with relapsed or refractory multiple myeloma (MM) 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

- As a single agent for the treatment of adult patients with relapsed or refractory MM who have received one or more lines of therapy.

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 Kyprolis is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of MM;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For relapsed or refractory disease, one of the following (a or b):
   a. Member has measurable disease as evidenced by one of the following assessed within the last 30 days (i, ii, or iii):
      i. Serum M-protein ≥ 0.5 g/dL;
      ii. Urine M-protein ≥ 200 mg/24 h;
      iii. Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal;
   b. Member has progressive disease, as defined by the IMWG response criteria (see *Appendix D*), assessed within 60 days following the last dose of the last anti-myeloma drug regimen received
5. For primary therapy, Kyprolis is prescribed in one of the following ways (a-d):*
   a. In combination with dexamethasone and Revlimid ® (lenalidomide)
   b. In combination with dexamethasone and cyclophosphamide;

c. In combination with dexamethasone, lenalidomide, and Darzalex® (daratumumab);
d. In combination with Sarclisa (isatuximab-irfc), lenalidomide with dexamethasone;

**Prior authorization may be required.*

6. For maintenance therapy, Kyprolis is prescribed in combination with lenalidomide;
7. For previously treated multiple myeloma for relapsed, refractory or progressive disease, Kyprolis is prescribed in one of the following ways (a-j):*
   a. In combination with dexamethasone or with Revlimid® (lenalidomide) plus dexamethasone in patients who have received one to three lines of therapy or if Velcade (bortezomib)-refractory *(see Appendix B for examples of prior therapy)*;
   b. As a single agent in patients who have received one or more lines of therapy;
   c. In combination with Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj) and dexamethasone in patients who have received one to three lines of therapy;
   d. In combination with Sarclisa (isatuximab-irfc) and dexamethasone in patients who have received one to three lines of therapy;
   e. In combination with Xpovio (selinexor) and dexamethasone in patients who have received one to three lines of therapy;
   f. In combination with dexamethasone and cyclophosphamide, with or without thalidomide, in patients who have received one to three lines of therapy;
   g. In combination with Polmalyst (pomalidomide) and dexamethasone in patients who have received one to three lines of therapy;;
   h. In combination with Bendeka (bendamustine) and dexamethasone for patients with relapse or refractory disease who have failed at least three prior therapies;
   i. In combination with Venclexta (venetoclax) and dexamethasone for patients with t(11:14) translocation;
   j. Other NCCN recommendations listed as category 1, 2A, or 2B;

   **Prior authorization may be required..*
8. For maintenance therapy for symptomatic multiple myeloma in combination with lenalidomide for transplant candidates who meets one of the following (a, b or c):
   a. Has had a previous response to primary myeloma therapy;
   b. Has had a response or has stable disease following an autologous hematopoietic cell transplant (HCT);
   c. Has had a response or has stable disease following a tandem autologous or allogeneic HCT for high risk;
9. Request meets one of the following (a, b, c, d, or e):
   a. Monotherapy: dose does not exceed 56 mg/m^2 twice weekly each 28-day cycle;
   b. With dexamethasone and Revlimid: dose does not exceed 27 mg/m^2 twice weekly 3 out of 4 weeks for twelve 28-day cycles, then 27 mg/m^2 twice weekly 2 out of 4 weeks for the next six 28-day cycles for up to a total of 18 cycles;
   c. With dexamethasone ± Darzalex: dose does not exceed (i or ii):
      i. 70 mg/m^2 once weekly each 28-day cycle;
      ii. 56 mg/m^2 twice weekly each 28-day cycle;
   d. With dexamethasone and Sarclisa: 56 mg/m^2 twice weekly each 28-day cycle;
   e. 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. Waldenstrom's Macroglobulinemia (Lymphoplasmacytic Lymphoma) (off-label) (must meet all)**:**
1. Diagnosis of Waldenstrom's macroglobulinemia (i.e., lymphoplasmacytic lymphoma) (WM/LPL);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed as a component of CaRD (carfilzomib, rituximab, and dexamethasone) regimen as primary or Kyprolis-relapsed therapy;
   **Prior authorization may be required.*
5. 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

C. Systemic Light Chain Amyloidosis (off-label) (must meet all)**:**
1. Diagnosis of Systemic Light Chain Amyloidosis;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request is for one of the following (a or b):
   a. Relapsed/refractory;
   b. Newly diagnosed disease;
5. Prescribed in one of the following ways (a or b):
   a. As a single agent;
   b. In combination with dexamethasone;
6. 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

D. 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. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA. PHARM.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, c, d or e):
   a. Monotherapy: new dose does not exceed 56 mg/m^2 twice weekly each 28-day cycle;
   b. With Revlimid plus dexamethasone: new dose does not exceed 27 mg/m^2 twice weekly 3 out of 4 weeks for twelve 28-day cycles, then 27 mg/m^2 twice weekly 2 out of 4 weeks for the next six 28-day cycles for up to a total of 18 cycles;
   c. With dexamethasone ± Darzalex: new does not exceed (i or ii):
      i. 70 mg/m^2 once weekly each 28-day cycle;
      ii. 56 mg/m^2 twice weekly each 28-day cycle;

d. With dexamethasone and Sarclisa: 56 mg/m^2 twice weekly each 28-day cycle;
e. 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. Waldenstrom's Macroglobulinemia (Lymphoplasmacytic Lymphoma) (off-label) (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA. PHARM.01) applies;
2. Member is responding positively to therapy;
3. 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

C. Systemic Light Chain Amyloidosis (off-label) (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit, or member has previously met all initial approval criteria or the Continuity of Care Policy (PA. PHARM.01) applies
2. Member is responding positively to therapy;
3. 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

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

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA. PHARM.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 policy – PA.CP.PMN.53 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CaRD: carfilzomib, rituximab, dexamethasone
FDA: Food and Drug Administration
FLC: free light chain
IMWG: International Myeloma Working Group
MM: multiple myeloma
NCCN: National Comprehensive Cancer Network
WM/LPL: Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma

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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Kyprolis (carfilzomib), Velcade® (bortezomib), Revlimid (lenalidomide), cyclophosphamide, dexamethasone	MM: Examples of primary therapy • Bortezomib/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone • Bortezomib/thalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab/lenalidomide/dexamethasone • Daratumumab/lenalidomide/bortezomib/ dexamethasone • Daratumumab/carfilzomib/lenalidomide/ dexamethasone • Daratumumab/cyclophosphamide/bortezomib/ dexamethasone • Daratumumab/bortezomib/thalidomide/ dexamethasone • Daratumumab/bortezomib/melphalan/prednisone • Dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide/bortezomib (VTD-PACE) • Ixazomib/cyclophosphamide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Lenalidomide/low-dose dexamethasone	Varies
Kyprolis (carfilzomib), Velcade® (bortezomib), Revlimid (lenalidomide), Darzalex® (daratumumab), Ninlaro® (ixazomib),	MM: Examples of therapy for previously treated for relapsed or refractory disease: • Bendamustine • Bendamustine/bortezomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • Bendamustine/carfilzomib/dexamethasone • Bortezomib/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Pomalyst (pomalidomide), Empliciti® (elotuzumab), Farydak (panobinostat), Thalomid® (thalidomide), bendamustine, cyclophosphamide, dexamethasone	• Carfilzomib/cyclophosphamide/dexamethasone • Carfilzomib/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Carfilzomib/cyclophosphamide/thalidomide/ dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Cyclophosphamide • Daratumumab • Daratumumab/bortezomib/dexamethasone • Daratumumab/carfilzomib/dexamethasone • Daratumumab/cyclophosphamide/bortezomib/ dexamethasone • Daratumumab/lenalidomide/dexamethasone • Daratumumab/pomalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin • Dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide/ +/- bortezomib • Elotuzumab/lenalidomide/dexamethasone • Elotuzumab/bortezomib/dexamethasone • Elotuzumab/pomalidomide/dexamethasone • Istatuximab-irfc/carfilzomib/dexamethasone • Ixazomib/cyclophosphamide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Ixazomib/pomalidomide/desamethasone • Isatuximab-irfc/pomalidomide/dexamethasone • Lenalidomide/dexamethasone Pomalidomide/bortezomib/dexamethasone • Pomalidomide/carfilzomib/dexamethasone • Pomalidomide/cyclophosphamide/dexamethasone • Pomalidomide/dexamethasone • Selinexor/bortezomib/dexamethasone • Selinexor/carfilzomib/dexamethasone • Selinexor/daratumumab/dexamethasone • Selinexor/opomalidomide/dexamthasone • Venetoclax/dexamethasone • Ideocabtagene vicleucel • Ciltacabtagene autoleucel • Teclistamab-cqyv	

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Rituxan (rituximab) Kyprolis (carfilzomib) dexamethasone	WM/LPL: CaRD (carfilzomib, rituximab, and dexamethasone)	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/Black Box Warnings
None reported

Appendix D: General Information

- The IMWG response criteria for multiple myeloma definition of progressive disease requires only one of the following:
  - Increase of 25% from lowest response value in any of the following:
    - Serum M-component (absolute increase must be ≥ 0.5 g/dL), and/or
    - Urine M-component (absolute increase must be ≥ 200 mg/24 h), and/or
  - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
  - Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥ 10%)
  - Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD (sum of the products of the maximal perpendicular diameters of measured lesions) of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis;
  - ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MM	Kyprolis + Dexamethasone: • Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles). o Cycle 1: administer Kyprolis 20 mg/m^2 on Day 1 and 70 mg/m^2 on Days 8 and 15 o Cycle 2 and later: 70 mg/m^2 on Day 1, 8, and 15 • Dose (once weekly 20/70 mg/m^2 regimen): o Starting dose of Kyprolis 20 mg/m^2 on Cycle 1, Day 1 o If tolerated, escalate Kyprolis to 70 mg/m^2 on Day 8 of Cycle 1.	70 mg/m^2

Indication	Dosing Regimen	Maximum Dose
	o Dexamethasone: 40 mg PO or IV on Days 1, 8, 15 of all 28-day cycles and on Day 22 of Cycles 1-9. <u>Kyprolis + Dexamethasone, OR **Monotherapy**:</u> • Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles). o Cycle 1: administer Kyprolis 20 mg/m^2 on Days 1 and 2, and 56 mg/m^2 on Day 8, 9, 15, and 16 o Cycle 2 and later: administer Kyprolis 56 mg/m^2 on Days 1, 2, 8, 9, 15 and 16 o For monotherapy: Cycle 13 and later: administer Kyprolis 56 mg/m^2 on Days 1, 2, 15 and 16 • Dose (twice weekly 20/56 mg/m^2 regimen): o Starting dose of Kyprolis 20 mg/m^2 on Cycle 1, Days 1 and 2 o If tolerated, escalate Kyprolis to 56 mg/m^2 on Day 8 of Cycle 1. <u>*Do not include if Monotherapy:*</u> o Dexamethasone: 20 mg PO or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle. <u>Kyprolis + Revlimid + Dexamethasone, OR **Monotherapy**:</u> • Cycles: Kyprolis IV as a 10-minute infusion for 28-day cycles. o Cycle 1: administer Kyprolis 20 mg/m^2 on Days 1 and 2, and 27 mg/m^2 on Days 8, 9, 15 and 16 o Cycle 2 to 12: administer Kyprolis 27 mg/m^2 on Days 1, 2, 8, 9, 15 and 16 o Cycle 13 and later, administer Kyprolis 27mg/m^2 on Day 1, 2, 15 and 16 o Discontinue Kyprolis after Cycle 18 and continue Revlimid and dexamethasone thereafter. • Dose (twice weekly 20/27 mg/m^2 regimen): o Starting dose of Kyprolis: 20 mg/m^2 on Cycle 1, Days 1 and 2 o If tolerated, escalate Kyprolis to 27 mg/m^2 on Day 8 of Cycle 1. <u>*Do not include if Monotherapy:*</u> o Revlimid: 25 mg PO QD on Days 1–21 of each cycle. o Dexamethasone: 40 mg PO or IV on Days 1, 8, 15, and 22 of each 28-day cycle. <u>Kyprolis + Darzalex + Dexamethasone:</u>	

Indication	Dosing Regimen	Maximum Dose
	Twice weekly 20/56 mg/m^2 regimen: • Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles). o Cycle 1: administer Kyprolis 20 mg/m^2 on Days 1 and 2 and 56 mg/m^2 on Days 8, 9, 15 and 16 o Cycle 2 and later: administer Kyprolis 56 mg/m^2 on Days 1, 2, 8, 9, 15 and 16 • Dose: o Starting dose of Kyprolis: 20 mg/m^2 on Cycle 1, Days 1 and 2 o If tolerated, escalate Kyprolis to 56 mg/m^2 on Day 8 of Cycle 1 o See prescribing information for Darzalex, Darzalex Faspro, and dexamethasone dosing. Once weekly 20/70 mg/m^2 regimen: • Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles). o Cycle 1: administer Kyprolis 20 mg/m^2 on Day 1 and 70 mg/m^2 on Days 8 and 15 o Cycle 2 and later: administer Kyprolis 70 mg/m^2 on Days 1, 8 and 15 • Dose: o Starting dose of Kyprolis: 20 mg/m^2 on Cycle 1, Days 1 and 2 o If tolerated, escalate Kyprolis to 70 mg/m^2 on Day 8 of Cycle 1 o See prescribing information for Darzalex, Darzalex Faspro, and dexamethasone dosing. __Kyprolis + Sarclisa + Dexamethasone: Twice weekly 20/56 mg/m^2 regimen: • Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles). o Cycle 1: administer Kyprolis 20 mg/m^2 on Days 1 and 2 and 56 mg/m^2 on Days 8, 9, 15 and 16 o Cycle 2 and later: administer Kyprolis 56 mg/m^2 on Days 1, 2, 8, 9, 15 and 16 • Dose: o Starting dose of Kyprolis: 20 mg/m^2 on Cycle 1, Days 1 and 2 o If tolerated, escalate Kyprolis to 56 mg/m^2 on Day 8 of Cycle 1 o See prescribing information for Sarclisa dosing___ _____	

Indication	Dosing Regimen	Maximum Dose
	Calculate the Kyprolis dose using the patient's actual body surface area at baseline. In patients with a body surface area greater than 2.2 m^2, calculate the dose based upon a body surface area of 2.2 m^2.	

VI. Product Availability

Single-dose vial: 10 mg, 30 mg, 60 mg

VII. References

1. Kyprolis Prescribing Information. Thousand Oaks: Onyx Pharmaceuticals, Inc.; June 2022. Available at: https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Kyprolis/kyprolis_pi.pdf. Accessed July 15, 2024.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 1, 2024.
3. National Comprehensive Cancer Network. Multiple Myeloma Version 04.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed August 1, 2024.
4. National Comprehensive Cancer Network. Waldenstrom's macroglobulinemia-lymphoplasmacytic lymphoma Version 02.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed August 1, 2024.
5. National Comprehensive Cancer Network. Systemic Light Chain Amyloidosis Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf. Accessed August 1, 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
J9047	Injection, carfilzomib, 1 mg

Reviews, Revisions, and Approvals	Date
New Policy Created	10/2018
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/2019
4Q 2020 annual review: Kyprolis dosing as monotherapy and in combination with dexamethasone added per PI; MM - FDA approved regimen added: in combination with Darzalex and dexamethasone, and NCCN recommended regimen added: in combination with dexamethasone and cyclophosphamide ± Thalomid; references reviewed and updated.	10/2020
4Q 2021 annual review: added primary therapy and revised therapy for previous treated for relapsed or refractory disease and updated Appendix B	10/2021

Reviews, Revisions, and Approvals	Date
Therapeutic Alternatives as per NCCN recommendation; updated Section V Dosage and Administration and Section VI Product Availability; references reviewed and updated.	
4Q 2022 annual review: RT4 – added new indication in combination with Sarclisa plus dexamethasone and Darzalex Faspro plus dexamethasone for MM after one to three lines of therapy; per NCCN Compendium added additional MM uses as primary therapy in combination with dexamethasone, lenalidomide, and Darzalex, added previously treated MM combination regimens, added criteria set for systemic light chain amyloidosis; references reviewed and updated.	10/2022
4Q 2023 annual review: updated MM initial approval criteria to include "for maintenance therapy, Kyprolis is prescribed in combination with lenalidomide" to align with current NCCN compendium and MM guidelines; for Appendix B, updated section with current MM primary therapies and previously treated for relapsed or refractory therapies per current	10/2023
4Q 2024 annual review: for relapse or refractory multiple myeloma prescribing regimens: added IMWG criterion defining progressive MM disease as MM class alignment, revised verbiage from "one or three lines of therapy" to "one to three lines of therapy", added verbiage "in patients who have received one to three lines of therapy" when used in combination with Xpovio, cyclophosphamide, or pomalidomide; for systemic light chain amyloidosis, references reviewed and updated.	10/2024