Clinical Policy: Carfilzomib (Kyprolis)

Reference Number: ERX.SPA.281
Effective Date: 12.01.18
Last Review Date: 11.21
Line of Business: Commercial, Medicaid

Revision Log

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

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
- 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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;
3. Age ≥ 18 years;
4. For primary therapy, Kyprolis is prescribed in one of the following ways (a or b):*
   a. In combination with dexamethasone and Revlimid® (lenalidomide);
   b. In combination with dexamethasone and cyclophosphamide;
5. For previously treated MM for relapsed or refractory disease, Kyprolis is prescribed in one of the following ways (a, b or c):*
   a. In combination with dexamethasone or with Revlimid (lenalidomide) plus dexamethasone in patients who have received one or three lines of therapy *(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) and dexamethasone in patients who have received one or three lines of therapy;

   **Prior authorization may be required.*
6. Request meets one of the following (a, b, c, or d):*
   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. 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. 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;
3. Age ≥ 18 years;
4. Prescribed as a component of CaRD (carfilzomib, Rituxan®* [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*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration: 6 months

C. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Kyprolis for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, c, or d):*
   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 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. 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. Waldenstrom's Macroglobulinemia (Lymphoplasmacytic Lymphoma) (off-label) (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Kyprolis for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, 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

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CaRD: carfilzomib, rituximab, dexamethasone
FDA: Food and Drug Administration
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/lenalidomide/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Daratumumab/lenalidomide/dexamethasone • Daratumumab/lenalidomide/bortezomib/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Carfilzomib/lenalidomide/dexamethasone	Varies
Kyprolis (carfilzomib), Velcade® (bortezomib), Revlimid (lenalidomide), Darzalex® (daratumumab), Ninlaro® (ixazomib), Pomalyst (pomalidomide), Empliciti® (elotuzumab), Farydak (panobinostat), Thalomid® (thalidomide), bendamustine, cyclophosphamide, dexamethasone	MM: Examples of therapy for previously treated for relapsed or refractory disease: • Bendamustine • Bortezomib/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Daratumumab/bortezomib/dexamethasone • Daratumumab/carfilzomib/dexamethasone • Daratumumab/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Pomalidomide/bortezomib/dexamethasone • Elotuzumab/lenalidomide/dexamethasone • Panobinostat/bortezomib/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Carfilzomib/dexamethasone • Pomalidomide/carfilzomib/dexamethasone • Carfilzomib/cyclophosphamide/thalidomide/dexamethasone • Panobinostat/carfilzomib	Varies

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/Boxed Warnings
None reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose

MM	Kyprolis + Dexamethasone:
	• Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles).
	  ○ Cycle 1: administer Kyprolis 20 mg/m^2 on Day 1 and 70 mg/m^2 on Days 8 and 15
	  ○ Cycle 2 and later: 70 mg/m^2 on Day 1, 8, and 15
	• Dose (once weekly 20/70 mg/m^2 regimen):
	  ○ Starting dose of Kyprolis 20 mg/m^2 on Cycle 1, Day 1
	  ○ If tolerated, escalate Kyprolis to 70 mg/m^2 on Day 8 of Cycle 1.
	  ○ Dexamethasone: 40 mg PO or IV on Days 1, 8, 15 of all 28-day cycles and on Day 22 of Cycles 1-9.
	
	Kyprolis + Dexamethasone, OR **Monotherapy**:
	• Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles).
	  ○ 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
	  ○ Cycle 2 and later: administer Kyprolis 56 mg/m^2 on Days 1, 2, 8, 9, 15 and 16
	  ○ 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):
	  ○ Starting dose of Kyprolis 20 mg/m^2 on Cycle 1, Days 1 and 2
	  ○ If tolerated, escalate Kyprolis to 56 mg/m^2 on Day 8 of Cycle 1.
	Do not include if Monotherapy:
	  ○ Dexamethasone: 20 mg PO or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle.
	
	Kyprolis + Revlimid + Dexamethasone, OR **Monotherapy**:
	• Cycles: Kyprolis IV as a 10-minute infusion for 28-day cycles.
	  ○ 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
	  ○ Cycle 2 to 12: administer Kyprolis 27 mg/m^2 on Days 1, 2, 8, 9, 15 and 16
	  ○ Cycle 13 and later, administer Kyprolis 27mg/m^2 on Day 1, 2, 15 and 16
	  ○ Discontinue Kyprolis after Cycle 18 and continue Revlimid and dexamethasone thereafter.
	• Dose (twice weekly 20/27 mg/m^2 regimen):
		70 mg/m^2

Indication	Dosing Regimen	Maximum Dose
	○ Starting dose of Kyprolis: 20 mg/m^2 on Cycle 1, Days 1 and 2 ○ If tolerated, escalate Kyprolis to 27 mg/m^2 on Day 8 of Cycle 1. *Do not include if Monotherapy:* ○ Revlimid: 25 mg PO QD on Days 1–21 of each cycle. ○ Dexamethasone: 40 mg PO or IV on Days 1, 8, 15, and 22 of each 28-day cycle. Kyprolis + Darzalex + Dexamethasone: Twice weekly 20/56 mg/m^2 regimen: • Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles). ○ 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 ○ Cycle 2 and later: administer Kyprolis 56 mg/m^2 on Days 1, 2, 8, 9, 15 and 16 • Dose: ○ Starting dose of Kyprolis: 20 mg/m^2 on Cycle 1, Days 1 and 2 ○ If tolerated, escalate Kyprolis to 56 mg/m^2 on Day 8 of Cycle 1 ○ See prescribing information for Darzalex and dexamethasone dosing. Once weekly 20/70 mg/m^2 regimen: • Cycles: Kyprolis IV as a 30-minute infusion (28-day cycles). ○ Cycle 1: administer Kyprolis 20 mg/m^2 on Day 1 and 70 mg/m^2 on Days 8 and 15 ○ Cycle 2 and later: administer Kyprolis 70 mg/m^2 on Days 1, 8 and 15 • Dose: ○ Starting dose of Kyprolis: 20 mg/m^2 on Cycle 1, Days 1 and 2 ○ If tolerated, escalate Kyprolis to 70 mg/m^2 on Day 8 of Cycle 1 ○ See prescribing information for Darzalex and dexamethasone dosing. *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.; March 2021. Available at: http://www.kyprolis.com. Accessed August 6, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 6, 2021.
3. National Comprehensive Cancer Network. Multiple Myeloma Version 07.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed August 6, 2021.
4. National Comprehensive Cancer Network. Waldenstrom's macroglobulinemia-lymphoplasmacytic lymphoma Version 01.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed August 6, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	08.07.18	11.18
4Q 2019 annual review: no significant changes; Kyprolis dosing as monotherapy and in combination with dexamethasone added per PI; references reviewed and updated.	08.20.19	11.19
4Q 2020 annual review: 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.	09.02.20	11.20
4Q 2021 annual review: added primary therapy and revised therapy for previous treated for relapsed or refractory disease and updated Appendix B Therapeutic Alternatives as per NCCN recommendation; updated Section V Dosage and Administration and Section VI Product Availability; references reviewed and updated.	08.06.21	11.21

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.