BlueCross BlueShield
Federal Employee Program
Federal Employee Program®
1310 G Street, N.W.
Washington, D.C. 20005
202.942.1000
Fax 202.942.1125

5.21.024

Section:	Prescription Drugs	**Effective Date:**	July 1, 2023
Subsection:	Antineoplastic Agents	**Original Policy Date:**	October 24, 2012
Subject:	Kyprolis	**Page:**	1 of 7

Last Review Date: June 15, 2023

Kyprolis

Description

Kyprolis (carfilzomib)

Background
Kyprolis (carfilzomib) is an antineoplastic agent for the treatment of multiple myeloma. Kyprolis works by inhibiting proteasome activity in blood and tissue, thereby delaying tumor growth of multiple myeloma, hematologic, and solid tumors (1).

Regulatory Status
FDA-approved indications: Kyprolis (carfilzomib) is a proteasome inhibitor indicated: (1-2)

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:
    a. Lenalidomide and dexamethasone; or
    b. Dexamethasone; or
    c. Daratumumab and dexamethasone; or
    d. Daratumumab and hyaluronidase-fihj and dexamethasone, or
    e. Isatuximab-irfc 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

Cardiac adverse reactions, including heart failure and ischemia, have occurred following administration of Kyprolis. Death due to cardiac arrest has occurred within a day of Kyprolis administration. Monitor for cardiac complications and manage promptly. Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. Thromboprophylaxis is recommended for patients being treated

with Kyprolis in combination with lenalidomide and dexamethasone; with dexamethasone; or with daratumumab and dexamethasone. Kyprolis in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma (1).

Kyprolis should be withheld or interrupted in patients with the following conditions, until the condition has been resolved or returned to baseline: (1)

1. Pulmonary arterial hypertension (PAH)
2. Pulmonary Toxicity, including Acute Respiratory Distress Syndrome, Acute Respiratory Failure, and Acute Diffuse Infiltrative Pulmonary Disease
3. Hypertension Including Hypertensive Crisis
4. Hemorrhage
5. Cardiac failure
6. Ischemia
7. Dyspnea
8. Tumor lysis syndrome (TLS)
9. Neutropenia
10. Thrombocytopenia
11. Hepatic toxicity and hepatic failure
12. Thrombotic Microangiopathy
13. Posterior Reversible Encephalopathy Syndrome (PRES)
14. Progressive Multifocal Leukoencephalopathy (PML)
15. Renal toxicity

Off-Label Use: (2)
The National Comprehensive Cancer Network (NCCN) Guidelines supports the off-label use of Kyprolis in the treatment of:

- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma as a neuropathy-sparing treatment option. Kyprolis must be used in combination with rituximab and dexamethasone (CaRD) regimen as primary therapy, or for relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response.

Infusion-related reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Dexamethasone should be administered prior to Kyprolis to reduce the incidence and severity of infusion-related reactions. Prior to receiving Kyprolis, patients must be well hydrated to reduce the risk of renal toxicity and of tumor lysis syndrome (TLS) (1).

Kyprolis can cause fetal harm. Female patients of reproductive potential should be advised to use effective contraception during treatment with Kyprolis and for at least 6 months following the

final dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Kyprolis and for 3 months following the final dose (1).

The safety and effectiveness of Kyprolis have not been established in pediatric patients (1).

Related policies
Ninlaro, Velcade

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Kyprolis may be considered **medically necessary** if the conditions indicated below are met.

Kyprolis may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Relapsed or refractory multiple myeloma (MM)

   AND ONE of the following:
   a. Patient has received one to three lines of multiple myeloma therapy **AND** used in combination with **ONE** of the following:
      a. Dexamethasone
      b. Lenalidomide plus dexamethasone
      c. Daratumumab plus dexamethasone
      d. Daratumumab and hyaluronidase-fihj plus dexamethasone
      e. Isatuximab-irfc plus dexamethasone
   b. Patient has received one or more lines of multiple myeloma therapy
      a. Used as a single agent

2. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
    a. Used in combination with rituximab and dexamethasone

AND ALL of the following for **ALL** indications:
- a. Female patients of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Kyprolis and for 6 months after the final dose
- b. Male patients with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Kyprolis and for 3 months after the final dose

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Relapsed or refractory multiple myeloma (MM)

    AND ONE of the following:
    - a. Used in combination with **ONE** of the following:
        a. Dexamethasone
        b. Lenalidomide plus dexamethasone
        c. Daratumumab plus dexamethasone
        d. Daratumumab and hyaluronidase-fihj plus dexamethasone
        e. Isatuximab-irfc plus dexamethasone
    - b. Used as a single agent

2. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
    a. Used in combination with rituximab and dexamethasone

AND ALL of the following for **ALL** indications:
- a. Patient must **NOT** have any disease progression or unacceptable toxicity
- b. Female patients of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Kyprolis and for 6 months after the final dose

c. Male patients with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Kyprolis and for 3 months after the final dose

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Kyprolis (carfilzomib) is an antineoplastic agent for the treatment of multiple myeloma. Kyprolis works by inhibiting proteasome activity in blood and tissue, thereby delaying tumor growth of multiple myeloma, hematologic, and solid tumors. Kyprolis has warnings for cardiac toxicities, acute renal failure, tumor lysis syndrome, pulmonary toxicity, hypertension, venous thrombosis, infusion-related reactions, hemorrhage, thrombocytopenia, hepatic toxicity and hepatic failure, thrombotic microangiopathy, posterior reversible encephalopathy syndrome, progressive multifocal leukoencephalopathy and embryo-fetal toxicity. The safety and effectiveness of Kyprolis have not been established in pediatric patients (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Kyprolis while maintaining optimal therapeutic outcomes.

References

1. Kyprolis [package insert]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc.; June 2022.
2. Sarclisa [package insert]. Bridgewater, NJ: Sanofi-aventis U.S. LLC; March 2021.
3. NCCN Drugs & Biologics Compendium® Carfilzomib 2023. National Comprehensive Cancer Network, Inc. Accessed on April 14, 2023.
4. NCCN Clinical Practice Guidelines in Oncology® Multiple Myeloma (Version 3.2023). National Comprehensive Cancer Network, Inc. December 2022. Accessed on April 14, 2023.

Policy History

Date	Action
October 2012	New Addition
December 2012	Annual editorial review and update
March 2014	Annual review
June 2015	Annual editorial review and reference update
January 2016	Addition of use in combination with dexamethasone or with lenalidomide plus dexamethasone in patient who have received one prior multiple myeloma therapy or as a single agent in patients who have received one prior multiple myeloma therapy and a new indication of Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma when used in combination with rituximab and dexamethasone. Removal of the requirement of patients who have received at least two prior therapies including Velcade (bortezomib) and an immunomodulator agent and have demonstrated disease progression on or within 60 days of completion of the last therapy Policy changed from 5.04.24 to 5.21.24
June 2016	Annual editorial review and reference update
September 2016	Annual review
June 2017	Annual review and reference update
June 2018	Annual review and reference update Update of criteria to match verbiage in package insert for the diagnosis of multiple myeloma
June 2019	Annual review and reference update
June 2020	Annual review and reference update
September 2020	Addition of indication: relapsed or refractory multiple myeloma in combination with daratumumab and dexamethasone in patients who have received one to three lines of therapy
December 2020	Annual review
April 2021	Addition of regimen: used in combination with isatuximab-irfc plus dexamethasone. Added contraception requirements for female and male patients. Revised renewal requirement to exclude patients with unacceptable toxicity.
June 2021	Annual editorial review
December 2021	Addition of regimen: used in combination with daratumumab and hyaluronidase-fihj plus dexamethasone

March 2022	Annual review and reference update
June 2023	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 15, 2023 and is effective on July 1, 2023.