Medical Drug Clinical Criteria

Subject:	Kyprolis (carfilzomib)		
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Overview

This document addresses the use of Kyprolis (carfilzomib). Kyprolis is a second generation proteasome inhibitor used for treatment of multiple myeloma and Waldenström's macroglobulinemia.

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. NCCN recommends Kyprolis in combination with dexamethasone and lenalidomide or in combination with daratumumab, lenalidomide, and dexamethasone as primary therapy for multiple myeloma. It also may be used in combination with pomalidomide, daratumumab (including daratumumab and hyaluronidase), or isatuximab for relapsed or 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 its use in relapsed or refractory non-cardiac disease.

Other Uses

NCCN also provides 2A recommendations for Kyprolis in newly diagnosed or relapsed or refractory multiple myeloma in combination with cyclophosphamide in certain regimens. Evidence for this regimen includes early phase I/II studies with small sample size. For newly diagnosed MM, carfilzomb was studied in combination with cyclophosphamide and dexamethasone in 58 participants (Bringhen 2014). A very good partial response (VGPR) was achieved by 71% with a 2 year overall survival of 87%. Severe cardiac events occurred in four participants and included heart failure, hypertension, and arrhythmia. The same combination was studied in older (≥65 year) transplant-ineligible patients with newly diagnosed MM (Bringhen 2018). Two year overall survival of 54 participants was 81%; grade 3-4 adverse event included neutropenia (22%) and cardiopulmonary toxicity (9%). The phase Ib/II CYKLONE trial studied cyclophosphamide, carfilzomib, thalidomide, and dexamethasone in transplant eligible newly diagnosed individuals (n=29) with 59% achieving VGPR after 4 cycles (Mikhael 2013). In the safety cohort (n=64), grade 3-4 adverse events included lymphopenia (38%), neutropenia (23%), and anemia (20%); four participants experienced grade 3-4 cardiac events. Additional NCCN recommendation for the combination use of Kyprolis and bendamustine for relapsed/refractory MM, and for the use of Kyprolis as maintenance therapy for transplant candidates have no supportive literature at this time.

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).

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.

Clinical Criteria

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.

Kyprolis (carfilzomib)

Requests for Kyprolis (carfilzomib) may be approved if the following criteria are met:

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)**; OR**
    ~~B.~~C. Treatment for relapsed or refractory disease for 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 panobinostat when the individual has received at least two prior therapies, including a proteasome inhibitor and an immunomodulatory agent (for example, lenalidomide or thalidomide) (NCCN 2A); **OR**~~
        ~~4.~~3. In combination with pomalidomide and dexamethasone when the individual has received at least two prior therapies, including a proteasome inhibitor and an immunomodulatory agent (for example, lenalidomide or thalidomide) (NCCN 2A); **OR**
        ~~5.~~4. In combination with daratumumab and dexamethasone; **OR**
        ~~6.~~5. In combination with isatuximab and dexamethasone.

OR
IV. Individual has a diagnosis of Waldenström's macroglobulinemia (NCCN 2A); **AND**
V. 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
VI. Individual has a diagnosis of Systemic Light Chain Amyloidosis (NCCN 2A); **AND**
VII. Individual has relapsed or refractory non-cardiac disease; **AND**
VIII. Carfilzomib is used as a single agent or in combination with dexamethasone.

Requests for Kyprolis (carfilzomib) may not be approved when the criteria above are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9047	Injection, carfilzomib, 1 mg [Kyprolis]

ICD-10 Diagnosis

C83.00-C83.09	Small cell B-cell lymphoma [lymphoplasmacytic lymphoma]

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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

Document History

Revised: 02/24/2023
Document History:

- 02/24/2023 – Annual Review: Remove combination use with panobinostat; add combination use with daratumumab, lenalidomide, and dexamethasone for newly diagnosed multiple myeloma per NCCN. Coding Reviewed: No changes.
- 02/25/2022 – Annual Review: Add criteria for systemic light chain amyloidosis per NCCN. Coding Reviewed: No changes.
- 05/21/2021 – Select Review: Update criteria to include use in combination with Sarclisa. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: Update references. Coding Reviewed: No changes.
- 02/21/2020– Annual Review: Update references; add biosimilar reference. Coding Review: No changes
- 05/17/2019– Annual Review: First review of Kyprolis clinical criteria. Add combination with pomalidomide and dexamethasone; minor wording and formatting updates. Add references for off-label criteria. Coding Reviewed: No changes.

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