



## Medical Policy Manual **Approved Revision: Do Not Implement until 9/30/21**

### Carfilzomib (Kyprolis®)

**NDC CODE(S)** 76075-0103-XX KYPROLIS 10MG Solution Reconstituted (AMGEN)  
76075-0102-XX KYPROLIS 30MG Solution Reconstituted (AMGEN)  
76075-0101-XX KYPROLIS 60MG Solution Reconstituted (AMGEN)

#### DESCRIPTION

Carfilzomib is a proteasome inhibitor. Proteasomes are found in the nucleus and cytoplasm of cells and are essential for cellular survival. They play a role in several complex cellular functions including the degradation of abnormal and misfolded proteins in the cell, involvement in the cell's stress response, cell cycle regulation, and cellular differentiation and also play a role in the immune system by generating antigenic peptides. Carfilzomib irreversibly binds to active sites of the core particle of the 26S proteasome. This action inhibits proteasome activity in blood and tissue leading to growth delay and cellular destruction in solid and hematologic tumor cells.

#### POLICY

- Carfilzomib for the treatment of the following is considered **medically necessary** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Multiple myeloma
  - Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
- Carfilzomib for the treatment of other conditions/diseases is considered **investigational**.

#### MEDICAL APPROPRIATENESS

##### INITIAL APPROVAL CRITERIA

Patient is at least 18 years of age; **AND**

##### Multiple Myeloma

- Used as primary therapy or for disease relapse after 6 months following primary induction therapy with the same regimen in patients with active (symptomatic) disease; **AND**
  - Used in combination with lenalidomide and dexamethasone; **OR**
  - Used in combination with dexamethasone and cyclophosphamide; **OR**
- Used for previously treated relapsed progressive or refractory disease; **AND**
  - Used as a single agent; **OR**
  - Used in combination with dexamethasone with or without lenalidomide; **OR**
  - Used in combination with dexamethasone and daratumumab; **OR**
  - Used in combination with dexamethasone and cyclophosphamide with or without thalidomide; **OR**
  - **Used in combination with dexamethasone and isatuximab-irfc; OR**
  - Used in combination with panobinostat; **AND**
    - Patient has received at least 2 prior regimens, including bortezomib and an immunomodulatory agent [i.e., lenalidomide, thalidomide, etc.]; **OR**
  - Used in combination with pomalidomide and dexamethasone; **AND**
    - Patient has received at least 2 prior therapies, including a proteasome inhibitor [i.e., bortezomib, etc.] and an immunomodulatory agent [i.e., lenalidomide, thalidomide, etc.]; **AND**
    - Disease has progressed on or within 60 days of completion of the last therapy

##### Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma



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- Used in combination with rituximab and dexamethasone (CaRD regimen); **AND**
  - Used as primary therapy; **OR**
  - Used for relapsed disease; **AND**
    - CaRD regimen was previously used as primary therapy; **AND**
    - Patient achieved a response from CaRD that lasted for at least 24 months

### RENEWAL CRITERIA

- Patient continues to meet indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in the Initial Approval Criteria; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: cardiac toxicity, pulmonary toxicity, pulmonary hypertension, dyspnea, severe infusion-related reactions, tumor lysis syndrome (TLS), thrombocytopenia, hepatic toxicity/failure, thrombotic microangiopathy (including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome [TTP/HUS]), acute renal failure, severe hypertension, posterior reversible encephalopathy syndrome (PRES), venous thromboembolic events, hemorrhage, progressive multifocal leukoencephalopathy (PML), etc.

### DOSAGE/ADMINISTRATION

INDICATION	DOSE
Multiple Myeloma	<p><u>20/27 regimen (single agent):</u></p> <ul style="list-style-type: none"> <li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 27 mg/m<sup>2</sup> on days 8, 9, 15, and 16 of a 28-day treatment cycle</li> <li>□ Cycles 2 through 12: 27 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li> <li>□ Cycle 13 and beyond: 27 mg/m<sup>2</sup> on days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li> </ul> <p><u>20/56 regimen (single agent):</u></p> <ul style="list-style-type: none"> <li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 56 mg/m<sup>2</sup> on days 8, 9, 15, and 16 of a 28-day treatment cycle.</li> <li>□ Cycles 2 through 12: 56 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li> <li>□ Cycle 13 and beyond: 56 mg/m<sup>2</sup> on days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li> </ul> <p><u>20/36 regimen for <b>NEWLY DIAGNOSED</b> disease (combination with lenalidomide and dexamethasone):</u></p> <ul style="list-style-type: none"> <li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 36 mg/m<sup>2</sup> days 8, 9, 15, and 16 of a 28-day treatment cycle</li> <li>□ Cycles 2 through 8: 36 mg/m<sup>2</sup> days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li> <li>□ Cycles 9 to 18: 36 mg/m<sup>2</sup> days 1, 2, 15, and 16 of a 28-day treatment cycle</li> </ul> <p><u>20/27 regimen for <b>RELAPSED/REFRACTORY</b> disease (combination with lenalidomide and dexamethasone):</u></p>



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	<ul style="list-style-type: none"><li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 27 mg/m<sup>2</sup> on days 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycles 2 through 12: 27 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycles 13 to 18: 27 mg/m<sup>2</sup> on days 1, 2, 15, and 16 of a 28-day treatment cycle; beginning with cycle 19, lenalidomide and dexamethasone may be continued (until disease progression or unacceptable toxicity) <b>without</b> carfilzomib</li></ul> <p><u>20/27 regimen (combination with pomalidomide and dexamethasone):</u></p> <ul style="list-style-type: none"><li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 27 mg/m<sup>2</sup> on days 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycles 2 through 6: 27 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycle 7 and beyond: 27 mg/m<sup>2</sup> on days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li><li>□ <b>NOTE:</b> If disease progression occurs while on maintenance dosing, resume full dosing of 27 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li></ul> <p><u>20/36 regimen (combination with pomalidomide and dexamethasone):</u></p> <ul style="list-style-type: none"><li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 36 mg/m<sup>2</sup> days 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycles 2 through 8: 36 mg/m<sup>2</sup> days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycle 9 and beyond: 36 mg/m<sup>2</sup> days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li></ul> <p><u>20/45 regimen (combination with panobinostat):</u></p> <ul style="list-style-type: none"><li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 45 mg/m<sup>2</sup> on days 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycle 2 and beyond: 45 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li></ul> <p><u>20/56 regimen (combination with dexamethasone):</u></p> <ul style="list-style-type: none"><li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 56 mg/m<sup>2</sup> on days 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycle 2 and beyond: 56 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li></ul> <p><u>20/70 regimen (combination with dexamethasone):</u></p> <ul style="list-style-type: none"><li>□ Cycle 1: 20 mg/m<sup>2</sup> on day 1; if tolerated, increase to 70 mg/m<sup>2</sup> on day 8 and 15 of a 28-day treatment cycle</li><li>□ Cycle 2 and beyond: 70 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li></ul> <p><u>20/36 regimen - <b>NEWLY DIAGNOSED</b> disease (combination with cyclophosphamide and dexamethasone):</u></p> <ul style="list-style-type: none"><li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 36 mg/m<sup>2</sup> days 8, 9, 15, and 16 of a 28-day treatment cycle</li><li>□ Cycles 2 through 9: 36 mg/m<sup>2</sup> days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li></ul>
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	<ul style="list-style-type: none"> <li>□ Cycle 10 and beyond: 36 mg/m<sup>2</sup> on days 1, 2, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li> </ul> <p><u>20/36 regimen for RELAPSED/REFRACTORY disease (combination with cyclophosphamide and dexamethasone):</u></p> <ul style="list-style-type: none"> <li>• Induction <ul style="list-style-type: none"> <li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 36 mg/m<sup>2</sup> days 8, 9, 15, and 16 of a 28-day treatment cycle</li> <li>□ Cycles 2 through 6: 36 mg/m<sup>2</sup> days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li> </ul> </li> <li>• Maintenance <ul style="list-style-type: none"> <li>□ Cycles 7 through 12: 36 mg/m<sup>2</sup> on days 1, 2, 15, and 16 of a 28-day treatment cycle</li> <li>□ Cycles 13 and beyond: 36 mg/m<sup>2</sup> on days 1 and 2 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li> </ul> </li> </ul> <p><u>20/56 regimen (combination with daratumumab and dexamethasone):</u></p> <ul style="list-style-type: none"> <li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 56 mg/m<sup>2</sup> on days 8, 9, 15 and 16 of a 28-day treatment cycle</li> <li>□ Cycle 2 and beyond: 56 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li> </ul> <p><u>20/70 regimen (combination with daratumumab and dexamethasone):</u></p> <ul style="list-style-type: none"> <li>□ Cycle 1: 20 mg/m<sup>2</sup> on day 1; if tolerated, increase to 70 mg/m<sup>2</sup> on day 8 and 15 of a 28-day treatment cycle</li> <li>□ Cycle 2 and beyond: 70 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</li> </ul> <p><u>20/56 regimen (combination with isatuximab-irfc and dexamethasone):</u>  <b>Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 56 mg/m<sup>2</sup> on days 8, 9, 15 and 16 of a 28-day treatment cycle</b>  <b>Cycle 2 and beyond: 56 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle; continue until disease progression or unacceptable toxicity</b></p> <p><u>20/36 regimen (combination with cyclophosphamide, thalidomide, and dexamethasone):</u></p> <ul style="list-style-type: none"> <li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1 and 2; if tolerated, increase to 36 mg/m<sup>2</sup> days 8, 9, 15, and 16 of a 28-day treatment cycle</li> <li>□ Cycles 2 through 4: 36 mg/m<sup>2</sup> days 1, 2, 8, 9, 15, and 16 of a 28-day treatment cycle</li> <li>□ Patients who achieve stable disease or better may continue treatment for up to 8 additional cycles</li> </ul>
Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma	<p><u>CaRD regimen (carfilzomib, rituximab, dexamethasone)</u></p> <ul style="list-style-type: none"> <li>• Induction <ul style="list-style-type: none"> <li>□ Cycle 1: 20 mg/m<sup>2</sup> on days 1, 2, 8 and 9 of a 21-day treatment cycle</li> <li>□ Cycles 2 through 6: 36 mg/m<sup>2</sup> on days 1, 2, 8 and 9 of a 21-day treatment; begin maintenance 8 weeks later</li> </ul> </li> </ul>



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	<ul style="list-style-type: none"> <li>• Maintenance <ul style="list-style-type: none"> <li>▫ 36 mg/m<sup>2</sup> on days 1 and 2 every 8 weeks for 8 cycles</li> </ul> </li> </ul>
<p><i>Note: 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<sup>2</sup>, calculate the dose based upon a body surface area of 2.2 m<sup>2</sup>.</i></p>	

### LENGTH OF AUTHORIZATION

Coverage will be provided for six months and may be renewed.

- Combination therapy with lenalidomide and dexamethasone as ~~subsequent~~ treatment in multiple myeloma is limited to eighteen (18) 28-day treatment cycles.
- Combination therapy with cyclophosphamide, thalidomide, and dexamethasone as subsequent treatment in multiple myeloma is limited to twelve (12) 28-day treatment cycles.
- Treatment of Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma is limited to six (6) 21-day induction therapy treatment cycles and eight (8) 56-day maintenance therapy treatment cycles.

### DOSING LIMITS

#### Max Units (per dose and over time) [HCPCS Unit]:

- Multiple Myeloma
  - 720 billable units every 28 days
- Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma
  - 320 billable units every 21 days

### APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

### IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

### ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).



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### SOURCES

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2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Carfilzomib. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed **May 2021**.
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19. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma Version 4.3.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed **May** 2021.
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**EFFECTIVE DATE** 9/30/2021

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