09-J1000-81

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Reviewed: 06/08/22

Revised: 08/15/22

Subject: Carfilzomib (Kyprolis®) Injection

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Carfilzomib (Kyprolis) is a tetrapeptide epoxy-ketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib has antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells. It was approved by the US Food and Drug Administration (FDA) in July 2012 for treatment of persons with multiple myeloma (MM) who have received at least 2 prior therapies, including bortezomib and an immunomodulatory drug, and demonstrated disease progression on or within 60 days of completion of the last therapy. In July 2014, the indication was expanded to include treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy when used in combination with lenalidomide and dexamethasone (i.e., triplet therapy). In addition, use as a single agent was added using the requirements of the original indication. In January 2016, the indication was again expanded to include use of carfilzomib in combination with dexamethasone as doublet therapy for relapsed or refractory MM. Also, use as a single agent was moved from third line to second-line treatment of relapsed or refractory MM. In August 2020, the indication of "treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy" was expanded to include carfilzomib treatment in combination with daratumumab (Darzalex) and dexamethasone. In April 2021, the indication for isatuximab (Sarclisa) was expanded to include "in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy". In June 2022, the carfilzomib label was updated to include this same regimen. Carfilzomib was previously granted orphan designation by the FDA for the treatment of MM in 2008.

Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. Although MM is typically sensitive to a variety of cytotoxic drugs, both as initial treatment or as treatment of relapsed disease, the durability of the response is transient

and a cure for MM remains elusive. Persons diagnosed with MM are classified as either having smoldering (asymptomatic) disease or symptomatic disease. Those classified with symptomatic MM are initially treated with primary therapy and in selected cases primary therapy is followed by high-dose chemotherapy with stem cell transplant (SCT). Therapy for previously treated MM will eventually be required for persons with relapsed disease after allogeneic or autologous SCT, primary progressive disease after initial allogeneic or autologous SCT, or persons who are non-transplant candidates who have progressive or relapsing disease after primary therapy.

The National Comprehensive Cancer Network (NCCN) Guidelines for Multiple Myeloma, Systemic Light Chain Amyloidosis, and Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma include carfilzomib regimens as recommended treatment options. For MM, carfilzomib is listed as first-line primary therapy [as triplet therapy in combination with dexamethasone and either lenalidomide or cyclophosphamide, or as quadruplet therapy in combination with daratumumab, lenalidomide, and dexamethasone (for transplant candidates only, and generally reserved for aggressive MM)] or as treatment for relapse/refractory disease [in various combination regimens]. For first-line primary therapy in both transplant and non-transplant candidates, bortezomib plus lenalidomide and dexamethasone is listed under "Preferred Regimens" (as a category 1 recommendation), while the carfilzomib-containing regimens are listed under "Other Recommended Regimens" or "Useful in Certain Circumstances" (as category 2A recommendations). For non-transplant candidates, daratumumab plus lenalidomide and dexamethasone is also listed under "Preferred Regimens" (as a category 1 recommendation). For primary therapy for Waldenström's Macroglobulinemia/Lymphoplasmacytic, carfilzomib is used as a component of the CaRD (carfilzomib, rituximab, and dexamethasone) regimen, and is listed as a category 2A recommendation under "Other Recommended Regimens". For previously treated systemic light chain amyloidosis, carfilzomib with or without dexamethasone, is listed as a category 2A recommendation under "Useful in Certain Circumstances" for non-cardiac amyloidosis only.

POSITION STATEMENT:

Note: For all dosage calculations the body surface area (BSA) should never exceed 2.2 m^2

The initiation of carfilzomib (Kyprolis) **meets the definition of medical necessity** for the following indications ("1", "2", "3", "4", and "5") when **ALL** of the associated criteria are met:

1. Primary therapy for previously untreated, symptomatic multiple myeloma (MM) when **ALL** of the following criteria are met ("a" to "d"):
    a. **ANY** of the following regimens will be used ("i", "ii". or "iii"):
        i. Carfilzomib will be used in combination with both lenalidomide (Revlimid) and dexamethasone
        ii. Carfilzomib will be used in combination with cyclophosphamide and dexamethasone
        iii. Carfilzomib will be used in combination with daratumumab (Darzalex/Darzalex Faspro), lenalidomide, and dexamethasone; **AND** the member is a transplant candidate*

        **This regimen is reserved for the treatment of aggressive MM only*

    b. A bortezomib-containing regimen is determined to be clinically inappropriate as first-line primary therapy for the member (the specific reason must be provided)

c. Carfilzomib will **NOT** be used in combination with another proteasome inhibitor [e.g., bortezomib or ixazomib (Ninlaro)].

d. The dosage does not exceed the following based on the medications used in combination:

i. With lenalidomide + dexamethasone (with or without daratumumab): 36 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle.

ii. With cyclophosphamide + dexamethasone: 36 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle.

2. Relapsed or refractory multiple myeloma when **ALL** of the following criteria are met ("a" to "d"):

a. The member has previously received one or more appropriate lines of therapy of adequate duration for the treatment of their MM

b. **ANY** of the following regimens will be used ("i" to "viii"):

i. Carfilzomib will be used in combination with dexamethasone as doublet therapy

ii. Carfilzomib will be used in combination with pomalidomide plus dexamethasone as triplet therapy (all requirements for the use of pomalidomide must also be met)

iii. Carfilzomib will be used in combination with lenalidomide plus dexamethasone as triplet therapy (all requirements for the use of lenalidomide must also be met)

iv. Carfilzomib will be used in combination with cyclophosphamide plus dexamethasone as triplet therapy

v. Carfilzomib will be used in combination with daratumumab plus dexamethasone as triplet therapy (all requirements for the use of daratumumab must also be met)

vi. Carfilzomib will be used in combination with isatuximab (Sarclisa) plus dexamethasone as triplet therapy (all requirements for the use of isatuximab must also be met)

vii. Carfilzomib will be used in combination with selinexor (Xpovio) plus dexamethasone as triplet therapy (all requirements for the use selinexor of must also be met)

viii. Carfilzomib will be used in combination with dexamethasone, cyclophosphamide and thalidomide as quadruple therapy (all requirements for the use of thalidomide must also be met)

c. Carfilzomib will **NOT** be used in combination with another proteasome inhibitor [e.g., bortezomib (Velcade) or ixazomib (Ninlaro)].

d. The dosage does not exceed the following based on the medications used in combination:

i. With cyclophosphamide + dexamethasone: 36 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.

ii. With lenalidomide + dexamethasone: 27 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle for the first 12 cycles. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.

iii. With dexamethasone: 56 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle until disease progression or unacceptable toxicity. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.

iv. With pomalidomide + dexamethasone: 27 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/ m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle until disease progression or unacceptable toxicity. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.

v. With daratumumab or isatuximab + dexamethasone: 56 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.

vi. With cyclophosphamide + thalidomide + dexamethasone: 36 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.

vii. With selinexor + dexamethasone: 27 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 56 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.

3. Systemic light chain amyloidosis (SLCA) when **ALL** of the following criteria are met ("a" to "f"):
   a. The diagnosis has been confirmed by the presence of amyloid deposits in tissue **AND** the deposits are composed of light chains
   b. Member has relapsed/refractory disease
   c. Member has non-cardiac disease
   d. Carfilzomib will be used as either monotherapy or combination with dexamethasone
   e. Carfilzomib will **NOT** be used in combination with another proteasome inhibitor [e.g., bortezomib (Velcade) or ixazomib (Ninlaro)]
   f. The dosage does not exceed 56 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle until disease progression or unacceptable toxicity. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.
4. Waldenström's macroglobulinemia (a.k.a., lymphoplasmacytic lymphoma) when **ALL** of the following criteria are met ("a" to "d"):
   a. Carfilzomib will be used in combination with **BOTH** rituximab (Rituxan) and dexamethasone (i.e., the CaRD regimen).
   b. **EITHER** of the following ("i" or "ii"):
      i. Primary therapy for previously untreated disease
      ii. Disease relapse if carfilzomib was previously used as primary therapy that was well tolerated and elicited a prolonged response

c. Carfilzomib will **NOT** be used in combination with another proteasome inhibitor [e.g., bortezomib (Velcade) or ixazomib (Ninlaro)]

d. The dosage does not exceed the following:

i. Cycles 1 to 6: 36 mg/ m^2 twice weekly for 2 weeks (4 doses total, e.g., days 1, 2, 8 and 9) of a 21-day cycle

ii. After cycle 6: 36 mg/ m^2 once daily for 2 days (2 total doses, e.g., days 1 and 2) of an 8-week cycle

5. Other FDA-approved or NCCN supported diagnosis (not previously listed above), and **BOTH** of the following ("a", "b", and "c"):

a. **EITHER** of the following is met:

i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage are recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. Carfilzomib is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis

c. The dosage of carfilzomib does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Approval duration: 6 months

The continuation of carfilzomib (Kyprolis) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. Authorization or reauthorization for carfilzomib has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of multiple myeloma, systemic light chain amyloidosis, Waldenström's macroglobulinemia, or other FDA-approved or NCCN supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria.
2. Member has **NOT** had disease progression during carfilzomib treatment
3. Carfilzomib will **NOT** be used in combination with another proteasome inhibitor [e.g., bortezomib (Velcade) or ixazomib (Ninlaro)].
4. The dosage does not exceed the following indication- and regimen-specific limits:

a. Primary therapy for previously untreated MM:

i. With lenalidomide + dexamethasone (with or without daratumumab):

- Cycles 1 to 8: 36 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/ m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle

- Cycles 9 and beyond: 36 mg/m^2 twice weekly every 2 weeks (weeks 1 and 3; 4 total doses, e.g., days 1, 2, 15 and 16) or 70 mg/ m^2 every 2 weeks (weeks 1 and 3; 2 total doses, e.g., days 1 and 15) of a 28-day cycle

ii. With cyclophosphamide + dexamethasone:

- 36 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle

b. Relapsed or refractory MM:

i. With lenalidomide + dexamethasone:

- Cycles 2 to 12: 27 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/ m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle
- Cycles 13 and beyond: 27 mg/m^2 twice weekly every 2 weeks (weeks 1 and 3; 4 total doses, e.g., days 1, 2, 15 and 16) or 70 mg/ m^2 every 2 weeks (weeks 1 and 3; 2 total doses, e.g., days 1 and 15) of a 28-day cycle

ii. With cyclophosphamide + dexamethasone:

- 36 mg/ m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/ m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle

iii. With dexamethasone:

- 56 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle

iv. With pomalidomide + dexamethasone:

- 27 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle

v. With daratumumab or isatuximab + dexamethasone:

- 56 mg/ m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/ m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle

vi. With cyclophosphamide + thalidomide + dexamethasone:

- 36 mg/ m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/ m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle

vii. With selinexor + dexamethasone:

- 27 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 56 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle. The first two doses (days 1 and 2) in week 1 should be 20 mg/m^2.

c. Waldenström's macroglobulinemia:

i. Cycles 1 to 6: 36 mg/m^2 twice weekly for 2 weeks (4 doses total, e.g., days 1, 2, 8 and 9) of a 21-day cycle.

ii. After cycle 6: 36 mg/m^2 once daily for 2 days (2 total doses, e.g., days 1 and 2) of an 8-week cycle.

d. Systemic light chain amyloidosis

- 56 mg/m^2 twice weekly for 21 days (6 total doses, e.g., days 1, 2, 8, 9, 15, and 16) or 70 mg/m^2 once weekly for 21 days (3 total doses, e.g., days 1, 8, and 15) of a 28-day cycle until disease progression or unacceptable toxicity.

e. Other FDA-approved or NCCN-supported diagnosis (not listed above) - the dosage of carfilzomib does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guideline for the specific diagnosis

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: carfilzomib in combination with dexamethasone, with daratumumab or daratumumab and hyaluronidase-fihj and dexamethasone, with isatuximab and dexamethasone, or with lenalidomide and dexamethasone is indicated for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. It is also indicated as a single agent for treatment of persons with relapsed or refractory multiple myeloma who have received one or more lines of therapy. The dose is calculated using the member's body surface area (BSA) at baseline. Members with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%. Thromboprophylaxis is recommended for patients being treated with the combination of carfilzomib, lenalidomide, and dexamethasone. There are numerous dosing regimens depending on if dexamethasone, daratumumab, and/or lenalidomide are given concurrently, and if the carfilzomib infusion is given over 10 minutes or 30 minutes. Please refer to the package insert for the specific dosage tables.

Dosage Modifications: View the product labeling for the recommend dose modification based on toxicities. No dosage adjustments are required in patients with renal impairment. Use in patients with hepatic impairment has not been evaluated. Patients with ALT/AST ≥3-times the upper limit of normal (ULN) and bilirubin ≥ 2-times the ULN were excluded from clinical trials. Patients with New York Heart Association Class III and IV heart failure were not eligible for the clinical trials, and safety in this population has not been evaluated.

Drug Availability: Carfilzomib is supplied as a 60-mg single-use vial of lyophilized powder that requires reconstitution. The vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F) and kept in the original package to protect from light.

PRECAUTIONS:

Boxed Warnings

- None

Contraindications

- None

Precautions/Warnings:

- **Cardiac adverse reactions including heart failure and ischemia**: New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of carfilzomib. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of carfilzomib administration. In randomized, open-label, multicenter trials for combination therapies, the incidence of cardiac failure events was 8% and that of arrythmias was 8% (majority of which were atrial fibrillation and sinus tachycardia). Monitor for cardiac complications. Treat promptly and withhold carfilzomib. In patients 75 years of age or older, the risk of cardiac failure is increased. Patients with NYHA Class III and IV heart failure, recent MI, conduction abnormalities, angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.

- **Acute renal failure**: Monitor serum creatinine regularly.

- **Pulmonary hypertension**: withhold dosing if suspected.

- **Pulmonary toxicity:** Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred. Discontinue is suspected.

- **Dyspnea**: monitor for and managed dyspnea immediately; interrupt carfilzomib until symptoms have resolved or returned to baseline.

- **Infusion reactions**: pre-medicate with dexamethasone to prevent or reduce severity. Advise members to seek immediate medical attention if symptoms develop.

- **Tumor lysis syndrome**: hydrate to prevent; monitor for tumor lysis syndrome and treat promptly.

- **Hypertension including hypertensive crisis**: Monitor blood pressure regularly. If hypertension cannot be adequately controlled, a risk-benefit decision on continued treatment is needed.

- **Venous thrombosis**: Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone, with intravenous daratumumab and dexamethasone, or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

- **Infusion-related Reactions**: Infusion-related reactions, including life-threatening reactions, have occurred in patients receiving carfilzomib. Signs and symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, laryngeal edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration. Premedicate with dexamethasone.

- **Hemorrhage**: Fatal or serious cases of hemorrhage may occur, including gastrointestinal, pulmonary, and intracranial hemorrhage. Promptly evaluate signs and symptoms of blood loss
- **Thrombocytopenia**: Monitor platelet counts. Platelet nadirs are observed between Day 8 and Day 15 of each 28-day cycle; reduce or interrupt dosing as clinically indicated.
- **Hepatic toxicity and hepatic failure**: monitor liver enzymes and withhold dosing if suspected.
- **Thrombotic microangiopathy**: cases including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) have been reported. Monitor for signs and symptoms of TTP/HUS. Discontinue therapy if suspected.
- **Posterior reversible encephalopathy syndrome (PRES)**: Consider neuro-radiological imaging (MRI) for onset of visual or neurological symptoms; discontinue carfilzomib if suspected.
- **Progressive Multifocal Leukoencephalopathy**: Consider PML if new or worsening neurologic manifestations. Discontinue carfilzomib in patients who develop PML.
- **Embryo-fetal toxicity**: carfilzomib can cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated. Previously designated as Pregnancy Category D.

BILLING/CODING INFORMATION:

HCPCS Coding

J9047	Injection, carfilzomib, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

C88.0	Waldenström macroglobulinemia
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse
E85.81	Light chain (AL) amyloidosis
E85.89	Other amyloidosis
E85.9	Amyloidosis, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Heavy chain – the larger component of an immunoglobulin. There are five types: IgG, IgA, IgM, IgD, and IgE.

Immunoglobulins (a.k.a., antibodies) – proteins made by normal plasma cells that have an important role in fighting infection as part of the humoral immune response. Antibodies are composed of two heavy chains and two light chains that form a larger complex. Each plasma cell produces only one type of heavy chain and one type of light chain.

Light chain – the smaller component of an immunoglobulin. There are two types: kappa and lambda.

Minimal response (MR) (according to the Revised Uniform Response Criteria by the International Myeloma Working Group) – **ALL** of the following:

- ≥25% but ≤49% reduction of serum M-protein
- Reduction in 24-hour urine M-protein by 50% to 89%
- In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required
- No increase in size or number of lytic bone lesions (development of compression fractures dose not exclude response).

Myeloma Protein (M-Protein) – a nonfunctional immunoglobulin protein or protein fragment produced by malignant plasma cells (or myeloma cells). Since myeloma cells are monoclonal, the M-proteins for a given patient are structurally identical. Both portions of an immunoglobulin (the heavy chain and light chain) can be found in the serum, while only light chains can be found in the urine.

Plasma cell - a fully differentiated B lymphocyte (a type of white blood cell) that is specialized for immunoglobulin production and is found primarily in bone marrow.

Primary refractory MM - patients who never achieve at least a MR to initial induction therapy and progress while on therapy

Progressive MM - at least a 25% increase from nadir in the serum M-protein (absolute increase must be ≥0.5 g/dL) or urine M-protein (absolute increase must be ≥200mg/24 hours), or in the difference between involved and uninvolved serum-free light-chain (FLC) levels (with an abnormal FLC ratio and FLC difference >100 mg/L).

Relapsed and refractory MM - patients who never achieve at least a MR or who progress within 60 days of their last therapy

Serum free light chain assay (SFLCA) – a test that detects the amount of unbound or free light chains (i.e., not attached to a heavy chain) in the serum. Normal values - kappa: 3.3 to 19.4 mg/L, lambda: 5.71 to 26.3 mg/L, kappa/lambda ratio: 0.26–1.65 (0.37–3.1 if renal impairment).

Serum Protein Electrophoresis (SPEP) – a test that detects and quantifies the amount of M-protein in the serum. An serum M-protein of greater than 30 g/L is consistent with a diagnosis of MM.

Smoldering (Asymptomatic) myeloma: defined as M-protein in serum of 30 g/dL or more and/or bone marrow clonal plasma cells of 10% or more, but no related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms.

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01
Bortezomib Injection, 09-J0000-92
Chimeric Antigen Receptor (CAR) T-Cell Therapies, 09-J3000-94
Daratumumab (Darzalex) Infusion and Daratumumab-Hyaluronidase-fihj (Darzalex Faspro) Injection, 09-J2000-49
Doxorubicin HCl Liposome (Doxil®) IV, 09-J0000-91
Elotuzumab (Empliciti) IV, 09-J2000-50
Isatuximab (Sarclisa) Injection, 09-J3000-67
Ixazomib (Ninlaro), 09-J2000-51
Oral Oncology Medications, 09-J3000-65
Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None

REFERENCES:

1. Berenson JR, Cartmell A, Bessudo A, et al. CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. Blood. 2016 Jun 30;127(26):3360-8. Epub 2016 May 12.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/08/22.

GUIDELINE UPDATE INFORMATION:

12/15/12	New Medical Coverage Guideline.
07/15/13	Review and revision to guideline; consisting of revising position statement to include current NCCN category 1 and 2A recommendations; revising description, dosage/administration, program exceptions and precautions sections; updating references.
01/01/14	Revision to guideline; consisting of code update.
07/15/14	Review and revision to guideline; consisting of updating references.
07/15/15	Review and revision to guideline; consisting of updating description, position statement, dosage/administration, precautions, coding/billing, and references.
09/15/15	Revision to guideline; consisting of updating description, position statement, dosage/administration, and references based on a new FDA-approved indication.
11/01/15	Revision: ICD-9 Codes deleted.
03/15/16	Revision to guidelines consisting of updating description, position statement, dosage/administration, and references based on expanded FDA-approved indications.
07/15/16	Review and revision to guideline consisting of updating description section, position statement, billing/coding information, definitions, related guidelines, and references.
12/15/16	Revision to guideline consisting of updating the description section, position statement, and references based on updated NCCN guidelines for multiple myeloma.
02/16/17	Revision: Update to Position Statement.
07/15/17	Review and revision to guidelines consisting of updating the description section, position statement, precautions, and references.
07/15/18	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, and references.
07/15/19	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, and references.

07/15/20	Review and revision to guidelines consisting of updating the description section, position statement, precautions, related guidelines, and references.
10/15/20	Revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, and references.
07/15/21	Review and revision to guidelines consisting of updating the description section, related guidelines, and references.
02/15/21	Revision to guideline consisting of updating the description section, position statement, and references based on updated NCCN guidelines for multiple myeloma.
07/15/22	Revision to guideline consisting of updating the description section, position statement, billing/coding, and references.
08/15/22	Revision to guideline consisting of updating the description section, dosage/administration, and references.