09-J3000-67

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Reviewed: 06/14/23

Revised: 07/15/23

Subject: Isatuximab-irfc (Sarclisa®) Infusion

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

DESCRIPTION:

Isatuximab (Sarclisa) is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody that binds to CD38, a transmembrane glycoprotein expressed on the surface of many hematopoietic cells and causes lysis of multiple myeloma cells. It was approved by the FDA in March 2020 for "in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor". In April 2021, the FDA approved an additional indication of "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". Isatuximab, as sponsored by the innovator drug company, previously received an orphan drug designation for the treatment of multiple myeloma (MM) in May 2014. Isatuximab was the second anti-CD38 antibody to be approved for the treatment of MM; the first being daratumumab (Darzalex) in November 2015.

The safety and efficacy of isatuximab leading to initial FDA approval was established in the ICARIA-MM trial (NCT02990338), a multicenter, multinational, randomized, open-label, 2-arm, phase 3 study in patients with relapsed and refractory MM. Patients had received at least two prior therapies including lenalidomide and a proteasome inhibitor. Patients were randomized to receive either isatuximab in combination with pomalidomide and low-dose dexamethasone (Isa-Pd, n=154), or pomalidomide and low-dose dexamethasone (Pd, n=153). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 67 years (range 36 to 86), 20% of patients were ≥75 years; 10% of patients entered the study with a history of COPD or asthma. The median number of prior lines of therapy was 3 (range 2 to 11) and 56% of patients received prior stem cell transplantation. The median duration of treatment was 41 weeks for Isa-Pd vs. 24 weeks for Pd. The primary efficacy endpoint was progression-free survival (PFS).

At a median follow-up of 11.6 months, Isa-Pd significantly prolonged median PFS vs. Pd (11.5 vs. 6.5 months; HR, 0.596 [95% CI, 0.44 to 0.81, p=0.001]. The PFS benefit was consistent across all subgroups, including patients with poor prognosis, aged 75 years or older, disease refractory to lenalidomide, a proteasome inhibitor, both lenalidomide and a proteasome inhibitor, or to lenalidomide at the last line prior to study entry. Overall response rate (ORR) [i.e., stringent complete response, complete response, very good partial response, or partial response] was significantly improved with the addition of isatuximab (60% vs, 35%, p<0.0001), as was the rate of very good partial response or better (32% vs 9%). Responses occurred faster (35 days vs. 58 days) and were more durable (13.3 months vs. 11.1 months) in the Isa-Pd group vs. the Pd group. Median overall survival (OS) was not reached for either treatment group. At the median follow-up time of 11.6 months, 43 (27.9%) patients on Isa-Pd and 56 (36.6%) patients on Pd had died; there was no significant difference in OS between treatments (HR, 0.687; 95% CI, 0.461 to 1.023). Isatuximab-pomalidomide-dexamethasone treatment led to greater incidence any grade infusion reactions (38% vs. 0%), upper respiratory infections (28% vs. 17%), diarrhea (26% vs. 20%), and bronchitis (24% vs. 9%); treatment related deaths occurred in 1 patient in the Isa-Pd group vs. 2 patients in the Pd group.

The National Comprehensive Cancer Network (NCCN) Guidelines for MM (Version 5.2023 – December 8, 2022) list the triplet drug regimens of isatuximab + carfilzomib (Kyprolis) + dexamethasone, and isatuximab + pomalidomide + dexamethasone under "Preferred Regimens for Early Relapse (1-3 prior therapies)" as category 1 recommendations for the treatment of previously treated MM. The regimens are listed under both the "Bortezomib-Refractory" and "Lenalidomide-Refractory" sections. The pomalidomide regimens are listed under a subsection of "After two prior therapies, including lenalidomide and a proteasome inhibitor".

POSITION STATEMENT:

Initiation of isatuximab (Sarclisa) **meets the definition of medical necessity** when **EITHER** of the following criteria is met ("1" or "2"):

1. The member has a diagnosis of symptomatic multiple myeloma (MM), and **ALL** of the following ("a" to "c"):
    a. Member has relapsed or refractory MM, and meets **EITHER** of the following ("i" or "ii"):
        i. Isatuximab will be used as triplet therapy in combination with both pomalidomide (Pomalyst) and dexamethasone for treatment of the member's MM, **AND** the member has received at least two appropriate prior therapies of adequate duration for the treatment of their MM that include an immunomodulatory agent (e.g., lenalidomide, thalidomide) and a proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib)
        ii. Isatuximab will be used as triplet therapy in combination with both carfilzomib (Kyprolis) and dexamethasone for treatment of the member's MM, **AND** the member has received at least one appropriate prior therapy of adequate duration for the treatment of their MM
    b. The member's MM was not previously refractory (i.e., disease progression on treatment or progression within 60 days after the last dose of a given therapy) to an isatuximab-containing treatment regimen

c. The member's dosage of isatuximab does not exceed 10 mg/kg (based on actual body weight) given more often than the following:
    - Cycle 1 (week 1 to 4): weekly (i.e., day 1, 8, 15, and 22) for 4 doses
    - Cycle 2 and beyond (week 5 and beyond): every 2 weeks (i.e., day 1 and 15 of each cycle)

2. Member has another FDA-approved or NCCN-supported diagnosis (not previously listed above), and **ALL** of the following are met ("a", "b", and "c"):
    a. **EITHER** of the following ("i" or "ii"):
        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. Isatuximab 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 isatuximab 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

Continuation of isatuximab (Sarclisa) **meets the definition of medical necessity** when **BOTH** of the following criteria are met ("1" and "2"):

1. An authorization or reauthorization for isatuximab has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of multiple myeloma, or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria
2. **EITHER** of the following based on the member's diagnosis ("a" or "b"):
    a. Multiple myeloma, and **ALL** of the following ("i", "ii", and "iii"):
        i. Isatuximab is being used in combination with pomalidomide and dexamethasone, **OR** in combination with carfilzomib and dexamethasone
        ii. The member's dosage of isatuximab does not exceed 10 mg/kg (based on actual body weight) given more often than the following:
            - Cycle 1 (week 1 to 4): weekly (i.e., day 1, 8, 15, and 22) for 4 doses
            - Cycle 2 and beyond (week 5 and beyond): every 2 weeks (i.e., day 1 and 15 of each cycle)
        iii. Member has not had disease progression during isatuximab treatment
    b. Other FDA-approved or NCCN-supported diagnosis (not listed above) and **ALL** of the following ("i", "ii", and "iii"):

i. The dosage of isatuximab 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

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

iii. The member has had a beneficial response to treatment with isatuximab

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

- Indicated (1) in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor, and (2) 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.
- The recommended dose 10 mg/kg actual body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone:
  - Cycle 1 - Days 1, 8, 15, and 22 (weekly)
  - Cycle 2 and beyond - Days 1, 15 (every 2 weeks)
- Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.
- Initiate antiviral prophylaxis to prevent herpes zoster reactivation based on standard guidelines.
- Pre-infusion medications are recommended. Refer to the product labeling for the specific medications and dosages.

Dose Adjustments

- **Adverse reactions**: Dosage adjustments are not recommended for adverse reactions. Adverse reactions are addressed with treatment interruption and slower infusion rates. Refer to the product labeling for recommendations on treatment interruption and infusion rate adjustments.
- **Renal impairment**: no dosage adjustment is necessary in patients with pre-existing renal impairment based on a population pharmacokinetic analysis.
- **Hepatic impairment**: no dosage adjustment is necessary in patients with pre-existing mild (total bilirubin level of 1 to 1.5 times the upper limit of normal (ULN) or AST level greater than the ULN) hepatic impairment based on a population pharmacokinetic analysis. Isatuximab has not been evaluated in patients with moderate (total bilirubin level 1.5 to 3 times the ULN and any AST level) or severe (total bilirubin level greater than 3 times the ULN and any AST level) hepatic impairment.

Drug Availability

- 100 mg/5 mL and 500 mg/25 mL single-dose vials
- Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not freeze. Do not shake.

PRECAUTIONS:

Boxed Warnings

- None

Contraindications

- Severe hypersensitivity to isatuximab or to any of its excipients

Precautions/Warnings

- **Infusion-Related Reactions**: In case of grade ≥2, interrupt isatuximab and manage medically. Permanently discontinue for grade 4 infusion-related reactions or anaphylactic reactions.
- **Neutropenia**: Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia delay isatuximab dose until neutrophil count recovery to at least $1.0x10^9$/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions are recommended.
- **Second Primary Malignancies (SPM)**: Monitor patients for the development of second primary malignancies.
- **Laboratory Test Interference:**
    - Interference with Serological Testing (Indirect Antiglobulin Test): Type and screen patients prior to starting treatment. Inform blood banks that a patient has received isatuximab
    - Interference with Serum Protein Electrophoresis and Immunofixation Tests: Isatuximab may interfere with the assays used to monitor M-protein, which may impact the determination of complete response.
- **Embryo-Fetal Toxicity**: Can cause fetal harm.

BILLING/CODING INFORMATION:

HCPCS Coding

J9227	Injection, isatuximab-irfc, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

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

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 Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: 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. A serum M-protein of greater than 30 g/L is consistent with a diagnosis of MM.

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01
Bortezomib Injection, 09-J0000-92
Carfilzomib (Kyprolis) IV, 09-J1000-81
Chimeric Antigen Receptor (CAR) T-Cell Therapies, 09-3000-94
Daratumumab (Darzalex) Infusion and Daratumumab-Hyaluronidase-fihj (Darzalex Faspro), 09-J2000-49
Doxorubicin HCl Liposome (Doxil) IV, 09-J0000-91
Elotuzumab (Empliciti) IV, 09-J2000-50
Ixazomib (Ninlaro), 09-J2000-51
Oral Oncology Medications, 09-J3000-65
Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None

REFERENCES:

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3. Dimopoulos MA, Leleu X, Moreau P, et al. Isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma patients with renal impairment: ICARIA-MM subgroup analysis. Leukemia. 2021 Feb;35(2):562-572. Epub 2020 May 23.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/14/23.

GUIDELINE UPDATE INFORMATION:

06/15/20	New Medical Coverage Guideline.
10/01/20	Revision: Added HCPCS code J9227 and removed code J9999.
05/15/21	Revision to guidelines consisting of updating the description, position statement, dosage/administration, precautions, related guidelines, and references based on a new FDA-approved indication.
07/15/21	Review and revision including updates to the description section, position statement, related guidelines, and references.
07/15/22	Review and revision to guidelines including updates to the description section and references.
07/15/23	Review and revision to guidelines including updates to the description section, related guidelines, and references.