09-J3000-67

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Subject: Isatuximab-irfc Intravenous Infusion (Sarclisa) and Subcutaneous Injection (Sarclisa Escena)

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

DESCRIPTION:

Isatuximab 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. Intravenous (IV) isatuximab (Sarclisa) was approved by the FDA in March 2020 “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”. In September 2024, the FDA approved another indication of “in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant (ASCT)”. In July 2026, a subcutaneously administered version of isatuximab (Sarclisa Escena) was approved by the FDA with similar indications as IV Sarclisa. The one difference in the indications is that Sarclisa Escena is approved in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior line of therapy (vs. two 2 prior therapies) including lenalidomide and a proteasome inhibitor. Unlike IV Sarclisa, Sarclisa Escena is administered as a fixed, non-weight-based subcutaneous dose of 1,400 mg with the CirCLIQ On-Body Delivery System (OBDS) or with a syringe and infusion set for manual administration. 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 IV Sarclisa 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 safety and efficacy of Sarclisa Escena leading to initial FDA approval was established in three randomized controlled trials – IRAKLIA (phase 3), IZALCO (phase 2), and IsaSoCu (phase 2). In IRAKLIA (NCT05405166), 531 patients with relapsed and/or refractory MM were randomized in a 1:1 ratio to receive either Sarclisa Escena 1,400 mg fixed dose as subcutaneous administration with OBDS device (Sarclisa Escena-Pd arm, 263 patients) or isatuximab-irfc as a 10 mg/kg IV infusion (IV isatuximab-irfc-Pd arm, 268 patients), in combination with pomalidomide and dexamethasone. Patients had received at least one prior therapy including lenalidomide and a proteasome inhibitor. Treatment was administered in both arms in 28-day cycles until disease progression or unacceptable toxicity. In both treatment arms, isatuximab-irfc was administered weekly in the first cycle and every two weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Dexamethasone orally 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 of each 28-day cycle. The median patient age was 66 years (range 31–86), 18% of patients were ≥75 years; 69% of patients were White, 21% Asian, and 4.1% Black or African American. The median weight was 72 kg (range: 36 to 161), with 32% of patients with a weight ≤65 kg, 44% with a weight >65 kg to ≤85 kg, and 24% with a weight >85 kg. The median number of prior lines of therapy was 2 (range 1 to 8) and 30% of patients had received 1 prior line of therapy. All patients except one received a prior proteasome inhibitor and prior lenalidomide, and 56% of patients received prior stem cell transplantation. Patients were previously exposed to daratumumab, in 14% of patients in Sarclisa Escena-Pd arm vs 11% in IV isatuximab-irfc-Pd arm. The majority of patients (84%) were refractory to lenalidomide, 50% to a proteasome inhibitor, and 44% to both an immunomodulator and a proteasome inhibitor.

The major efficacy measures were ORR as assessed by an Independent Review Committee, based on central laboratory data for M-protein and central radiologic imaging review using the International Myeloma Working Group (IMWG) criteria and the pharmacokinetic endpoint of C_{trough} at steady state (corresponding to pre-dose at Cycle 6 Day 1). The results show that Sarclisa Escena 1,400 mg administered subcutaneously in combination with Pd is non-inferior to isatuximab-irfc 10 mg/kg administered IV in combination with Pd in terms of ORR and C_{trough} at steady state. Results are presented in Table below.

	Sarclisa Escena-Pd (n=263)	**IV isatuximab-irfc-Pd (n=268)**
ORR (sCR, CR, VGPR or PR); n (%)	187 (71.1%)	189 (70.5%)
[95% CI]	1.008 [0.903 to 1.126]	
Stringent complete response (sCR) + Complete response (CR); n (%)	47 (17.9%)	55 (20.5%)

Very good partial response (VGPR); n (%)	75 (28.5%)	68 (25.4%)
Partial response (PR); n (%)	65 (24.7%)	66 (24.6%)
Systemic administration reaction	1.5% (0.4% Grade 3 or 4)	25% (1.1% Grade 3 or 4)

The National Comprehensive Cancer Network (NCCN) Guidelines for MM (Version 5.2026 - January 9, 2026) lists the quadruplet regimen of isatuximab + lenalidomide + bortezomib + dexamethasone as a category 1 recommendation for Primary Therapy for HCT Candidates under the section of "Preferred". The quadruplet regimen of isatuximab + lenalidomide + carfilzomib + dexamethasone is listed as a category 2A recommendation for Primary Therapy for HCT Candidates under the section of "Other Recommended". The other preferred category 1 regimen for Primary Therapy for HCT Candidates is daratumumab + lenalidomide + bortezomib + dexamethasone. For Primary Therapy if HCT-deferred or if HCT is not indicated, the quadruplet regimen of isatuximab + lenalidomide + bortezomib + dexamethasone is listed as a category 1 preferred regimen for patients <80 years old who are not frail. The quadruplet regimen of isatuximab + lenalidomide + carfilzomib + dexamethasone is listed as a category 2B recommendation for Primary Therapy if HCT-deferred or if HCT is not indicated under the section of "Useful In Certain Circumstances". For this same patient population, the triplet regimen of isatuximab + lenalidomide + dexamethasone is listed as a category 2A recommendation under "Other Recommended". For relapse/refractory disease, the triplet drug regimens of isatuximab + carfilzomib + dexamethasone, and isatuximab + pomalidomide + dexamethasone are listed under Relapsed/Refractory Disease After 1 - 3 Prior Therapies and "Preferred Regimens" 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:

Drug Waste Reduction: Additional medical necessity criteria for dose optimization may apply to IV Sarclisa depending on the requested dose and member's benefit. Refer to Medical Coverage Guideline Drug Waste Reduction, 09-J5000-54.

Site of Care: If isatuximab-irfc (Sarclisa, Sarclisa Escena) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J5000-59, Site of Care Policy for Select Oncology Medications.

Initiation of intravenous isatuximab (Sarclisa) or subcutaneous isatuximab (Sarclisa Escena) **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. **ANY** of the following ("i", "ii", or "iii"):
        i. Member has newly diagnosed and previously untreated symptomatic MM, **AND BOTH** of the following ("1" and "2")
            1. Member is both eligible for a hematopoietic cell transplant (HCT) (i.e., a transplant candidate) and planning to receive a HCT
            2. Isatuximab will be used as primary therapy in combination with **EITHER** lenalidomide, bortezomib, and dexamethasone; **OR** lenalidomide, carfilzomib, and dexamethasone
        ii. Member has newly diagnosed and previously untreated* symptomatic MM, **AND BOTH** of the following ("1" and "2")
            1. A hematopoietic cell transplant (HCT) is either **NOT** indicated (i.e., a non-transplant candidate) or **NOT** planned (i.e., transplant-deferred)
            2. **ANY** of the following ("a", "b", or "c"):

a. Isatuximab will be used as primary therapy in combination with lenalidomide and dexamethasone

b. **BOTH** of the following ("i" and "ii"):

i. Isatuximab will be used as primary therapy in combination with lenalidomide, bortezomib, and dexamethasone

ii. Member is less than 80 years old **AND** not frail

c. **BOTH** of the following ("i" and "ii"):

i. Isatuximab will be used as primary therapy in combination with lenalidomide, ixazomib (Ninlaro), and dexamethasone, **AND** the member had intolerable adverse effects (e.g., severe neuropathy) to bortezomib - the specific adverse effect(s) must be provided

ii. Member is less than 80 years old **AND** not frail

**Exception permitted if using an ixazomib regimen due to bortezomib adverse effects*

iii. Member has relapsed or refractory MM, and meets **EITHER** of the following ("i" or "ii"):

1. 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 **ONE** appropriate prior line of therapy 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)

2. 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 dosage of IV isatuximab does not exceed 10 mg/kg (based on actual body weight) or the dosage of subcutaneous isatuximab does not exceed 1,400 mg given more often than the following:

- If used as primary therapy for newly diagnosed MM in members eligible for a hematopoietic cell transplant **AND** in combination with lenalidomide, bortezomib, and dexamethasone (cycles are 6 weeks):
  - Cycle 1 (week 1 to 6): weekly (i.e., day 1, 8, 15, 22 and 29) for 5 doses
  - Cycle 2 and 3 (week 7 to 18): every 2 weeks (i.e., day 1, 15, and 29 of each cycle)
  - After cycle 3 (week 19): Stop for high-dose chemotherapy and hematopoietic cell transplant. Additional doses every 2 weeks are appropriate if the member's transplant is delayed.
- If used as primary therapy for newly diagnosed MM in members eligible for a hematopoietic cell transplant **AND** in combination with lenalidomide, carfilzomib, and dexamethasone (cycles are 4 weeks):
  - Cycles 1 and 2 (week 1 to 8): weekly (i.e., day 1, 8, 15, and 22) for 8 doses
  - Cycles 3 to 6 (week 9 to 24): every 2 weeks (i.e., day 1 and 15 of each cycle)
  - Cycles 7 and 8 (weeks 25 to 32): every 4 weeks (i.e., day 1 of each cycle)
  - After cycle 8 (week 32): Stop for high-dose chemotherapy and hematopoietic cell transplant. Additional doses every 4 weeks are appropriate if the member's transplant is delayed.

- If used as primary therapy for newly diagnosed MM when a hematopoietic cell transplant is either **NOT** indicated (i.e., a non-transplant candidate) or **NOT** planned (i.e., transplant-deferred):
    - If used in combination with bortezomib (or ixazomib), lenalidomide, and dexamethasone:
        - For IV isatuximab (6- and 4-week treatment cycles)
            - Cycle 1 (42-day cycle, week 1 to 6) - Days 1, 8, 15, 22, and 29
            - Cycles 2 to 4 (42-day cycles, week 7 to 25) - Days 1, 15 and 29 (every 2 weeks)
            - Cycles 5 to 17 (28-day cycles, week 26 to week 72) - Days 1 and 15 (every 2 weeks)
            - Cycles 18 and beyond (28-day cycles) - Day 1 (every 4 weeks)
        - For subcutaneous isatuximab (4-week treatment cycles)
            - Cycle 1 (week 1 to 4) - Days 1, 8, 15, and 22 (weekly)
            - Cycles 2 to 12 (week 5 to 48) - Days 1 and 15 every 2 weeks)
            - Cycles 13 and beyond – Day 1 (every 4 weeks)
    - If used in combination with lenalidomide, and dexamethasone (cycles are 4 weeks):
        - 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)
- If used for relapsed or refractory MM (cycles are 4 weeks):
    - 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 [except if used as primary therapy for newly diagnosed MM in members eligible for a hematopoietic cell transplant **AND** in combination with lenalidomide, carfilzomib, and dexamethasone – approve for 12 months]

Continuation of isatuximab (Sarclisa) or subcutaneous isatuximab (Sarclisa Escena) **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 relapsed or refractory multiple myeloma (MM), primary therapy for MM in a member when a HCT is either not indicated or not planned [for primary therapy for newly diagnosed MM in members eligible for a hematopoietic cell transplant – see initiation criteria] 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 **ANY** of the following:
            - lenalidomide and dexamethasone
            - pomalidomide and dexamethasone,
            - carfilzomib and dexamethasone
            - bortezomib, lenalidomide, and dexamethasone
            - ixazomib, lenalidomide, and dexamethasone
        ii. The dosage of IV isatuximab does not exceed 10 mg/kg (based on actual body weight) or the dosage of subcutaneous isatuximab does not exceed 1,400 mg given more often than the following depending on the regimen used:
            - When in combination with lenalidomide and dexamethasone, in combination with pomalidomide and dexamethasone, or in combination with carfilzomib and dexamethasone (4-week treatment cycles):
                - 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)
            - When in combination with bortezomib (or ixazomib), lenalidomide, and dexamethasone
                - For IV isatuximab (6- and 4-week treatment cycles)
                    - Cycle 1 (42-days, week 1 to 6) - Days 1, 8, 15, 22, and 29
                    - Cycles 2 to 4 (42-days, week 7 to 25) - Days 1, 15 and 29 (every 2 weeks)
                    - Cycles 5 to 17 (28-days, week 26 to week 72) - Days 1 and 15 (every 2 weeks)
                    - Cycles 18 and beyond (28-day cycles) - Day 1 (every 4 weeks)
                - For subcutaneous isatuximab (4-week treatment cycles)
                    - Cycle 1 (week 1 to 4) - Days 1, 8, 15, and 22 (weekly)
                    - Cycles 2 to 12 (week 5 to 48) - Days 1 and 15 every 2 weeks)
                    - Cycles 13 and beyond – Day 1 (every 4 weeks)
        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

Sarclisa

- 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, (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, and (3) in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are NOT eligible for autologous stem cell transplant (ASCT).
- The recommended dose is 10 mg/kg actual body weight administered as an intravenous infusion
  - When in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone (28-day treatment cycles):
    - Cycle 1 - Days 1, 8, 15, and 22 (weekly)
    - Cycles 2 and beyond - Days 1, 15 (every 2 weeks)
  - When in combination with bortezomib, lenalidomide, and dexamethasone (42- and 28-day treatment cycles)
    - Cycle 1 (42-day cycle) - Days 1, 8, 15, 22, and 29
    - Cycles 2 to 4 (42-day cycles) - Days 1, 15 and 29 (every 2 weeks)
    - Cycles 5 to 17 (28-day cycles) - Days 1 and 15 (every 2 weeks)
    - Cycles 18 and beyond (28-day cycles) - Day 1 (every 4 weeks)
- Initiate antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) if needed based on standard guidelines
- Pre-infusion medications are recommended. Refer to the product labeling for the specific medications and dosages.

Sarclisa Escena

- Indicated (1) in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor, (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, and (3) in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are NOT eligible for autologous stem cell transplant (ASCT).
- The recommended dose is 1,400 mg administered as a subcutaneous injection with the CirCLIQ On-Body Delivery System (OBDS) or with a syringe and infusion set for manual administration

- When in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone (28-day treatment cycles):
  - Cycle 1 - Days 1, 8, 15, and 22 (weekly)
  - Cycles 2 and beyond - Days 1, 15 (every 2 weeks)
- When in combination with bortezomib, lenalidomide, and dexamethasone (28-day treatment cycles):
  - Cycle 1 - Days 1, 8, 15, and 22 (weekly)
  - Cycles 2 to 12 - Days 1 and 15 every 2 weeks)
  - Cycles 13 and beyond (28-day cycles) – Day 1 (every 4 weeks)

- Initiate antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) if needed based on standard guidelines
- Pre-infusion medications are recommended. Refer to the product labeling for the specific medications and dosages.

Dose Adjustments

Sarclisa and Sarclisa Escena

- **Adverse reactions**: Dosage adjustments are not recommended for adverse reactions. Adverse reactions are addressed with treatment interruption and/or 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, including end-stage renal disease (ESRD) or on dialysis, 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

Sarclisa

- 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.

Sarclisa Escena

- 1,400 mg/10 mL (140 mg/mL) single-dose vial
- Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light until 20 minutes prior to use. Do not freeze. Do not shake.
- The CirCLIQ OBDS (Filling Base and Wearable On-Body Injector for single use) is packaged separately

PRECAUTIONS:

Sarclisa and Sarclisa Escena

Boxed Warnings

- None

Contraindications

- Severe hypersensitivity to isatuximab or to any of its excipients

Precautions/Warnings

- **Hypersensitivity and Other Administration Reactions:** In case of grade ≥2 systemic administration-related reactions (SARs), interrupt isatuximab and manage medically. For IV isatuximab, the infusion rate should be slowed to half the initial infusion rate when re-initiated (refer to the package labeling). Permanently discontinue isatuximab for grade 4 SAR or anaphylactic reactions. In clinical trials (ICARIA-MM, IKEMA, and IMROZ), in patients treated with IV isatuximab (N=592), infusion-related reactions occurred in 34.8% of patients (Grade 1: 6%, Grade 2: 28%, Grade 3 or 4: 1.2%). In clinical trials (IRAKLIA, IZALCO, and IsaSoCu), in patients treated with SQ isatuximab (N=411), infusion-related reactions occurred in 3.2% of patients (Grade 1: 2.2%, Grade 2: 0.7%, Grade 3: 0.2%). For SQ isatuximab, injection site reactions were reported in 9% (8% Grade 1 and 1.5% Grade 2) of patients and in 0.86% of injections (refer to the package labeling for recommendations).
- **Infections:** Isatuximab can cause serious and fatal infections. Monitor patients for signs and symptoms of infection and treat appropriately.
- **Neutropenia**: Monitor complete blood cell counts periodically during treatment. Consider the use of antibacterial 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. Advise patients of the potential risk to a fetus and to use effective contraception

BILLING/CODING INFORMATION:

HCPCS Coding

J9227	Injection, isatuximab-irfc, 10 mg
J9999	Not otherwise classified, antineoplastic drugs (for Sarclisa Escena ONLY)

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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

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
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
Elranatamab-bcmm (Elrexfio) Injection, 09-4000-64
Linvoseltamab (Lynozyfic) IV Infusion, 09-J5000-27
Oncology Self-Administered Medications, 09-J3000-65
Talquetamab-tgvs (Talvey) Injection, 09-J4000-63
Teclistamab (Tecvayli) Injection, 09-J4000-46
Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None

REFERENCES:

1. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet 2019; 394(10214):2096-2107.
2. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2026. https://www.clinicalkey.com/pharmacology/. Accessed 07/30/26.
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.
4. Facon T, Dimopoulos MA, Leleu XP, et al.; IMROZ Study Group. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024 Oct 31;391(17):1597-1609. Epub 2024 Jun 3.
5. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2026 Jul 30]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/.

6. Goldschmidt H, Mai EK, Bertsch U, et al: Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. Lancet Haematol 2022; 9(11):e810-e821
7. Leypoldt LB, Tichy D, Besemer B, et al. Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma. J Clin Oncol. 2024 Jan 1;42(1):26-37. Epub 2023 Sep 27.
8. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 07/30/26.
9. Moreau P, Dimopoulos MA, Yong K, et al. Isatuximab plus carfilzomib/dexamethasone versus carfilzomib/dexamethasone in patients with relapsed/refractory multiple myeloma: IKEMA Phase III study design. Future Oncol. 2020 Jan;16(2):4347-4358. Epub 2019 Dec 13.
10. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 07/30/26.
11. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Multiple Myeloma (Version5.2026 – January 9, 2026). Available at http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf. Accessed 07/30/26.
12. Ocio EM, Parmar G, Mateos MV, et al. Review of the first on-body injector (OBI) for the subcutaneous delivery of an oncology drug: isatuximab in multiple myeloma. Expert Opin Drug Deliv. 2026 Jul;23(7):1289-1303.
13. O'Donnell E, Mo C, Yee AJ, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone in patients with newly diagnosed, transplantation-eligible multiple myeloma (SKylaRk): a single-arm, phase 2 trial. Lancet Haematol. 2024 Jun;11(6):e415-e424. Epub 2024 Apr 24.
14. Parmar G, Capra M, Seguro F, et al. Efficacy and safety of isatuximab subcutaneous plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma: results of the Phase 2 study IZALCO. Blood Cancer J. 2025 Dec 27;16(1):16
15. Sarclisa (Isatuximab-irfc injection, for intravenous use) [package insert]. Morristown, NJ: Sanofi-Aventis U.S. LLC. June 2026.
16. Sarclisa Escena (isatuximab-irfc injection, solution) [package insert]. Morristown, NJ: Sanofi-Aventis U.S. LLC. July 2026.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/12/26.

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.

07/15/24	Review and revision to guideline consisting of updating the description, position statement, related guidelines, and references. New quadruplet regimen of isatuximab + lenalidomide + bortezomib + dexamethasone added as a covered use for newly diagnosed MM members eligible for an autologous stem cell transplant.
12/15/24	Revision to guidelines consisting of updating the description, position statement, dosage/administration, precautions, and references based on a new FDA-approved indication and NCCN recommendations.
07/15/25	Review and revision to guideline consisting of updating the description, position statement, and references. Standardized the transplant candidate language. For the quadruplet regimen of isatuximab + lenalidomide + bortezomib + dexamethasone for transplant candidates, added requirements of less than 80 years of age and not frail (per NCCN guidelines).
06/01/26	Revision: Added Drug Waste Reduction statement to the Position Statement.
07/01/26	Revision: Added Site of Care statement to the Position Statement.
07/15/26	Review and revisions of guidelines consisting of updates to the description, position statement, related guidelines and references. Added isatuximab in combination with lenalidomide and dexamethasone as an appropriate primary therapy option when a HCT is not indicated or not planned.
09/15/26	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding information, and references, based on the inclusion of subcutaneous Sarclisa Escena.