SARCLISA® (isatuximab-irfc) injection, for intravenous use

Initial U.S. Approval: 2020

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use SARCLISA safely and effectively. See full prescribing information for SARCLISA.

**SARCLISA** (isatuximab-irfc) injection, for intravenous use

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**RECENT MAJOR CHANGES**

Indications and Usage (1)

3/2021

Dosage and Administration (2.1, 2.2, 2.5)

3/2021

Warnings and Precautions (5.1, 5.2, 5.3, 5.4)

3/2021

**INDICATIONS AND USAGE**

SARCLISA is a CD38-directed cytolytic antibody indicated:

• in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

• 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. (1)

**DOSAGE AND ADMINISTRATION**

Premedicate with dexamethasone, acetaminophen, H2 antagonists, and diphenhydramine.

The recommended dose of SARCLISA is 10 mg/kg actual body weight administered as an intravenous infusion every week for 100 mg/5 mL (20 mg/mL) solution in single-dose vial (3)

**DOSE FORMS AND STRENGTHS**

Injection:

• 100 mg/5 mL (20 mg/mL) solution in single-dose vial (3)

• 500 mg/25 mL (20 mg/mL) solution in single-dose vial (3)

**CONTRAINDICATIONS**

Patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients (4)

**WARNINGS AND PRECAUTIONS**

- Infusion-Related Reactions: In case of grade ≥3, interrupt SARCLISA and manage medically. Permanently discontinue for grade 4 infusion-related reactions or anaphylactic reaction. (5.1)

- Neutropenia: Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. SARCLISA dose delays and the use of colony-stimulating factor may be required to allow improvement of neutrophil count. (5.2)

- Second Primary Malignancies (SPM): Monitor patients for the development of second primary malignancies. (5.3)

- 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 SARCLISA. (5.4, 7.1)
  - Interference with Serum Protein Electrophoresis and Immunofixation Tests: SARCLISA may interfere with the assays used to monitor M-protein, which may impact the determination of complete response. (5.4, 7.1)

- Embryo-Fetal Toxicity: Can cause fetal harm. (5.5)

**ADVERSE REACTIONS**

In combination with pomalidomide and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea. The most common hematology laboratory abnormalities (≥20%) were decreased hemoglobin, decreased neutrophils, decreased lymphocytes, and decreased platelets. (6.1)

In combination with carfilzomib and dexamethasone: The most common adverse reactions (≥20%) were infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain. The most common hematology laboratory abnormalities (≥20%) were decreased hemoglobin, decreased lymphocytes, and decreased platelets. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2021

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carfilzomib and Dexamethasone

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Days</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>1, 8, 15, and 22 (weekly)</td>
<td></td>
</tr>
<tr>
<td>Cycle 2 and beyond</td>
<td>15 (every 2 weeks)</td>
<td></td>
</tr>
</tbody>
</table>

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

SARCLISA is used in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone. For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies (14) and manufacturer’s prescribing information.

Missed SARCLISA Doses

If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

2 Recommended Premedications

Administer the following premedications prior to SARCLISA infusion to reduce the risk and severity of infusion-related reactions (see Warnings and Precautions (5.1)):

• When administered in combination with SARCLISA and pomalidomide: Dexamethasone 40 mg orally or intravenously (or 20 mg orally or intravenously for patients ≥75 years of age).
When administered in combination with SARCILISA and carfilzomib: Dexamethasone 20 mg (intravenously on the days of SARCILISA and/or carfilzomib infusions, orally on day 2 in cycle 2 and beyond, and orally on day 23 in all cycles).

- Acetaminophen 650 mg to 1,000 mg orally (or equivalent).
- H2 antagonists
- Diphenhydramine 25 mg to 50 mg orally or intravenously (or equivalent). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (orally or intravenously) corresponds to the dose to be administered before infusion as part of the premedication and part of the backdose treatment. Administer dexamethasone before SARCILISA and pomalidomide and before SARCILISA and carfilzomib administration.

Administer the recommended premedication agents 15 to 60 minutes prior to starting a SARCILISA infusion.

2.3 Dose Modifications

No dose reduction of SARCILISA is recommended. Dose delay may be required to allow recovery of blood counts in the event of hematological toxicity [see Warnings and Precautions (5.2, 5.4)]. For information concerning drugs given in combination with SARCILISA, see manufacturer’s prescribing information.

2.4 Preparation

Prepare the solution for infusion using aseptic technique as follows:

Calculate the dose (mg) of required SARCILISA based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly) [see Dosage and Administration (2.1)]. More than one SARCILISA vial may be necessary to obtain the required dose for the patient.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Remove the volume of diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diltuent bag that is equal to the required volume of SARCILISA injection.
- Withdraw the necessary volume of SARCILISA injection from the vial and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride ( PVC) with d(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenize the diluted solution by inverting the bag. Do not shake.

2.5 Administration

- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set
- Prepare the solution for infusion using aseptic technique as follows:
  - Calculate the dose (mg) of required SARCILISA based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly) [see Dosage and Administration (2.1)]. More than one SARCILISA vial may be necessary to obtain the required dose for the patient.
  - Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
  - Remove the volume of diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diltuent bag that is equal to the required volume of SARCILISA injection.
  - Withdraw the necessary volume of SARCILISA injection from the vial and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
  - The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride ( PVC) with d(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
  - Gently homogenize the diluted solution by inverting the bag. Do not shake.

- Following administration, administer the SARCILISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of the infusion rate should be considered only in the absence of infusion-related reactions [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

**Table 2: Infusion Rates of SARCILISA Administration**

<table>
<thead>
<tr>
<th>Infusion Rates of SARCILISA Administration</th>
<th>Dilution Volume</th>
<th>Initial Rate</th>
<th>Absence of Infusion-Related Reaction</th>
<th>Rate Increment</th>
<th>Maximum Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First infusion</td>
<td>250 mL</td>
<td>25 mL/hour</td>
<td>For 60 minutes</td>
<td>25 mL/hour</td>
<td>150 mL/hour</td>
</tr>
<tr>
<td>Second infusion</td>
<td>250 mL</td>
<td>50 mL/hour</td>
<td>For 30 minutes</td>
<td>50 mL/hour</td>
<td>200 mL/hour</td>
</tr>
<tr>
<td>Subsequent infusions</td>
<td>250 mL</td>
<td>200 mL/hour</td>
<td></td>
<td></td>
<td>200 mL/hour</td>
</tr>
</tbody>
</table>

3 DOSE FORMS AND STRENGTHS

SARCILISA is a clear to slightly opalescent, colorless to slightly yellow solution, essentially free of visible particulates available as:

- Injection: 100 mg/5 mL (20 mg/mL) in a single-dose vial
- Injection: 500 mg/25 mL (20 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

SARCILISA is contraindicated in patients with severe hypersensitivity to ixazomib-irf or to any of its excipients [see Warnings and Precautions (5.1)].

5 ADVERSE REACTIONS

5.1 Infusion-Related Reactions

Serious infusion-related reactions including life-threatening anaphylactic reactions have occurred with SARCILISA treatment. Severe signs and symptoms included cardiac arrest, hypertension, hypotension, respiratory distress, anaphylactic reactions, or anaphylactic shock. Serious infusion-related reactions including life-threatening anaphylactic reactions have occurred with SARCILISA treatment. Severe signs and symptoms included cardiac arrest, hypertension, hypotension, respiratory distress, anaphylactic reactions, or anaphylactic shock.

5.2 Neutropenia

In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3-4 neutropenia occurred in 85% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (25%), defined as infection with concurrent grade ≥3 neutropenia. Neutropenic complications occurred in 28% of patients, including febrile neutropenia (11%) and neutropenic infections (17%) [see Adverse Reactions (6.1)]. 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 grade 4 neutropenia delay SARCILISA dose until neutrophil count recovery to at least 1.0 x 10^9/L and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCILISA are recommended.

5.3 Second Primary Malignancies

The incidence of second primary malignancies is increased in patients treated with SARCILISA-containing regimens. The overall incidence of second primary malignancies in all the SARCILISA-exposed patients was 3.6%. In ICARIA-MM, second primary malignancies occurred in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm.

In ICARIA-MM, second primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm. The most common (≥1%) second primary malignancies in ICARIA-MM and IKEMA (N=329) included skin cancers (4% with SARCILISA-containing regimens and 1.5% with comparative regimens) and solid tumors other than skin cancer (1.8% with SARCILISA-containing regimens and 1.5% with comparative regimens). All patients with skin cancer have continued treatment after resection of the skin cancer.

Monitor patients for the development of second primary malignancies.

5.4 Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)

Interference with reactivity with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an interference with Serological Testing (Indirect Antiglobulin Test)

5.5 Second Primary Malignancies

Second primary malignancies were reported at a rate of 0.1% in the first cycle and every two weeks thereafter, in combination with pomalidomide and dexamethasone (Isa-Pd) (n=152) or pomalidomide and dexamethasone (Pd) (n=149) [see Clinical Studies (14)]. Among patients receiving Isa-Pd, 66% were exposed to SARCILISA for 6 months or longer and 24% were exposed for greater than 12 months or longer.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions from SARCILISA are also described in other sections of the labeling:

- Infusion-Related Reactions [see Warnings and Precautions (5.1)]
- Neutropenia [see Warnings and Precautions (5.2)]
- Second Primary Malignancies [see Warnings and Precautions (5.3)]
- Laboratory Test Interference

- Neutropenia

- Second Primary Malignancies

- Laboratory Test Interference

- Neutropenia

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- Second Primary Malignancies

- Laboratory Test Interference

- Neutropenia
Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions in >5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

Permanent treatment discontinuation due to an adverse reaction (grades 1–4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2.6%). SARCLISA alone was discontinued in 3% of patients due to infusion-related reactions.

Dose interruptions due to an adverse reaction occurred in 31% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was infusion-related reaction (28%). The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea.

Table 3 summarizes the adverse reactions in ICARIA-MM.

Table 4: Hematology Laboratory Abnormalities During the Treatment Period in Patients Receiving Isa-Pd in ICARIA-MM Trial

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin decreased</td>
<td>99 32 0</td>
<td>97 28 0</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>96 24 61</td>
<td>92 38 31</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>92 42 13</td>
<td>92 35 8</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>84 14 16</td>
<td>79 9 15</td>
</tr>
</tbody>
</table>

The denominator used to calculate the percentages was based on the safety population.

CTCAE version 4.03
*Infusion-related reaction includes infusion-related reaction, cytokine release syndrome, and drug hypersensitivity.
†Upper respiratory tract infection includes bronchitis, bronchitis viral, chronic sinusitis, fungal pneumonia, influenza-like illness, laryngitis, nasopharyngitis, parainfluenza virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
‡Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilius, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jiroveci pneumonia.
§Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

Table 4 summarizes the hematologic laboratory abnormalities in ICARIA-MM.
Table 6 summarizes the hematology laboratory abnormalities in IKEMA.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA + Carfilzomib + Dexamethasone ( Isa-Kd) (N=177)</th>
<th>Carfilzomib + Dexamethasone (Kd) (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%) Grade 4 (%)</td>
<td>Grade 3 (%) Grade 4 (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>99 22 0</td>
<td>99 20 0</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>94 52 17</td>
<td>95 43 14</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>94 19 11</td>
<td>88 16 8</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>55 18 17</td>
<td>43 7 0</td>
</tr>
</tbody>
</table>

The denominator used to calculate the percentage was based on the safety population.

### Description of Selected Adverse Reactions

#### Infection

In ICARIA-MM, infection-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58% (38 patients) treated with SARCLISA. All patients who experienced infection-related reactions received treatment during the 1st infusion of SARCLISA, with 3 patients (2%) also having infection-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infection-related reactions were reported in 3.9%, grade 2 in 32%, grade 3 in 1.3%, and grade 4 in 1.3% of the patients. Signs and symptoms of grade 3 or 4 infection-related reactions included dyspnea, hypertension, and bronchospasm. The incidence of infection interruptions because of infection-related reactions was 30%. The median time to infusion interruption was 55 minutes. SARCLISA was discontinued in 2.6% of patients due to infection-related reactions.

In IKEMA, infection-related reactions were reported in 81 patients (46%) treated with Isa-Kd. Grade 1 infection-related reactions were reported in 14%, grade 2 in 32%, and grade 3 in 0.6% of the patients treated with Isa-Kd. Signs and symptoms of grade 3 infection-related reactions included dyspnea and hypertension. SARCLISA was discontinued in 0.6% of patients due to infection-related reactions [see Warnings and Precautions (5.1)].

In a separate study (TCD14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all grade 2) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the infection-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

#### Infusion-related reactions

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In a separate study (TCD14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all grade 2) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

#### Cardiac failure

In IKEMA, cardiac failure (including cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure, and pulmonary edema) was reported in 7.3% of patients with the Isa-Kd group (grade ≥3 in 4%) and in 6.6% of patients with the Kd group (grade ≥3 in 4.1%). Serious cardiac failure was observed in 4% of patients in the Isa-Kd group and in 3.3% of patients in the Kd group. See the current prescribing information for carfilzomib for more information.

### 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA can activate natural killer (NK) cells in the absence of CD38-positive target tumor cells dependent cytotoxicity (CDC). Isatuximab-irfc inhibits the ADP-ribosyl cyclase activity of CD38.

### 6.3 Interference with Serological Testing

SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antigen tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA [see Warnings and Precautions (5.4)].

### 7 DRUG INTERACTIONS

#### 7.1 Laboratory Test Interference

**Serological Testing:** SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antigen tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA [see Warnings and Precautions (5.4)].

**Interference with Serotonin Prophylaxis and Immunochemical Tests:** SARCLISA may be incidentally detected by serum protein electrophoresis and immunofluorescence assays used for the monitoring of M-protein and may interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria [see Warnings and Precautions (5.4)].
12.2 Pharmacodynamics

In multiple patients treated with SARCLISA combined with pomalidomide and dexamethasone, a decrease in absolute counts of total NK cells (including inflammatory CD16+ bright CD56− dim) and cytotoxic CD16+ bright CD56− dim NK cells and CD19+ B cells was observed in peripheral blood.

Cardiac Electrophysiology

Up to 2 times the approved recommended dose, SARCLISA does not prolong the QT interval to any clinically relevant extent.

A relationship between isatuximab-irfc exposure and overall response rate and progression-free survival was observed. No apparent relationship was observed between an increase of isatuximab-irfc exposure and adverse reactions.

12.3 Pharmacokinetics

Following administration of isatuximab-irfc in combination with pomalidomide and dexamethasone at the recommended dose and schedule, the steady-state mean (CV%) predicted maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) of isatuximab-irfc were 351 µg/mL (36.0%) and 72,600 µg·h/mL (51.7%), respectively.

Following administration of isatuximab-irfc in combination with carfilzomib and dexamethasone at the recommended dose and schedule, the steady-state mean (CV%) predicted Cmax for carfilzomib and AUC of isatuximab-irfc were 665 µg/mL (30.8%) and 159,000 µg·h/mL (37.1%), respectively.

The median time to reach steady state of isatuximab-irfc was 18 weeks with a 3-1-fold accumulation. Isatuximab-irfc AUC increases in greater than dose proportional manner overall a dosage range from 1 mg/kg to 20 mg/kg (0.1 to 2 times the approved recommended dosage) every 2 weeks. Isatuximab-irfc AUC increases proportionally over a dosage range from 5 mg/kg to 20 mg/kg (0.5 to 2 times the approved recommended dosage) every week for 4 weeks followed by every 2 weeks.

Distribution

The mean (CV%) predicted total volume of distribution of isatuximab-irfc is 6.8 L (26.2%).

Metabolism

Isatuximab-irfc is expected to be metabolized into small peptides by catabolic pathways.

Elimination

Isatuximab-irfc total clearance decreased with increasing dose and with multiple doses. At steady state, the near elimination (≥99%) of isatuximab-irfc from plasma after the last dose is predicted to occur in approximately 2 months. The elimination of isatuximab-irfc was similar when given as a single agent or as combination therapy.

Specific Populations

The following factors have no clinically meaningful effect on the exposure of isatuximab-irfc: age (36 to 85 years, 70 patients were ≥75 years old), sex, renal impairment (eGFR <30 mL/min/1.73 m²), and mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or total bilirubin >1.5 to 3 × ULN and any AST) and severe (total bilirubin >3 × ULN and any AST) hepatic impairment on isatuximab-irfc pharmacokinetics is unknown.

No dose adjustments are recommended in these specific patient populations.

Body weight

The clearance of isatuximab-irfc increased with increasing body weight.

Race

White (n=377, 79%) or Asian (n=25, 5%) race have no clinically meaningful effect on the exposure of isatuximab-irfc. The effect of Black (n=18, 4%) race on the exposure of isatuximab-irfc is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and genotoxicity studies have not been conducted with isatuximab-irfc. Fertility studies have not been conducted with isatuximab-irfc.

14 CLINICAL STUDIES

Multiple Myeloma

ICARIA-MM

The efficacy and safety of SARCLISA in combination with pomalidomide and dexamethasone (Isa-Pd) were evaluated in ICARIA-MM (NCT02990038), a multicenter, multinational, randomized, open-label, 2-arm, phase 3 study. Patients were eligible for inclusion if they had an Eastern Cooperative Oncology Group (ECOG) status of 0–2; platelets ≥75,000 cells/µL, absolute neutrophil count ≥1 × 10⁹/L, creatinine clearance ≥50 mL/min/1.73 m² (MDRD formula), AST ≤ ULN, and ALT ≤ ULN. A total of 307 patients were randomized in a 1:1 ratio to receive either SARCLISA in combination with pomalidomide and dexamethasone (Isa-Pd, 154 patients) or pomalidomide and dexamethasone (Pd, 153 patients). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicities. SARCLISA 10 mg/kg was administered as an intravenous infusion weekly in the first cycle and every two weeks thereafter. Pomalidomide 4 mg was taken orally once daily from the first cycle and every two weeks thereafter. Carfilzomib was administered as an intravenous infusion at the dose of 20 mg/m² on days 1 to 21 of each 28-day cycle. Dexamethasone (orally or intravenously) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle.

Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 67 years (range 36–89), 28% of patients were ≥75 years; 79% of patients were White, 12% Asian, and 1% Black or African American; 10% of patients entered the study with a history of COPD or asthma. The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) was 34%. The International Staging System (ISS) stage at study entry was I in 37%, II in 30%, and III in 33% of patients. Overall, 26% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(14;14) and t(14;16) were present in 12%, 8% and 2% of patients, respectively.

The median number of prior lines of therapy was 3 (range 2–11). All patients received a prior proteasome inhibitor, and 56% of patients received a prior lenalidomide and/or a proteasome inhibitor, and 73% to both an immunomodulator and a proteasome inhibitor.

The median duration of treatment was 41 weeks for Isa-Pd group compared to 24 weeks for Pd group.

The median time to first response in responders was 35 days in the Isa-Pd group versus 58 days in the Pd group. The median duration of response was 13.5 months (95% CI: 10.6–14.9) in the Isa-Pd group versus 11.1 months (95% CI: 8.6–14.4) in the Pd group. Median overall survival was not reached for either treatment group. At a median follow-up time of 11.6 months, 43 (27.9%) patients on Isa-Pd and 56 (36.6%) patients on Pd had died. The OS results at interim analysis did not reach statistical significance.

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The mean (CV%) predicted total volume of distribution of isatuximab-irfc is 6.8 L (26.2%).
impairment (eGFR < 60 mL/min/1.73 m²) was 24% in the Isa-Kd group versus 15% in the Kd group. The International Staging System (ISS) stage at study entry was I in 53%, II in 31%, and III in 15% of patients. Overall, 24% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(14;16), or t(4;14) were present in 11%, 14%, and 2% of patients, respectively. In addition, gain(1q21) was present in 42% of patients.

The median number of prior lines of therapy was 2 (range 1–4) with 44% of patients who received 1 prior line of therapy. Overall, 90% of patients received prior proteasome inhibitors, 78% received prior immunomodulators (including 43% who received prior lenalidomide), and 61% received prior stem cell transplantation. Overall, 33% of patients were refractory to prior proteasome inhibitors. 45% were refractory to prior immunomodulators (including 33% refractory to lenalidomide), and 21% were refractory to both a proteasome inhibitor and an immunomodulator.

The median duration of treatment was 80 weeks for the Isa-Kd group compared to 61 weeks for the Kd group.

The efficacy of SARCLISA was based upon PFS. PFS results were assessed by an Independent Review Committee based on central laboratory data for M-protein and central radiologic imaging review using the IMWG criteria. The improvement in PFS represented a 45% reduction in the risk of disease progression or death in patients treated with Isa-Kd compared to patients treated with Kd.

Efficacy results are presented in Table 8 and Kaplan-Meier curves for PFS are provided in Figure 2. The data support the hypothesis that Isa-Kd is better than Kd in terms of PFS. The improvement in PFS represented a 45% reduction in the risk of disease progression or death in patients treated with Isa-Kd compared to patients treated with Kd. Overall, 90% of patients received prior proteasome inhibitors, 78% received prior immunomodulators (including 43% who received prior lenalidomide), and 61% received prior stem cell transplantation. Overall, 33% of patients were refractory to prior proteasome inhibitors. 45% were refractory to prior immunomodulators (including 33% refractory to lenalidomide), and 21% were refractory to both a proteasome inhibitor and an immunomodulator. The median duration of treatment was 80 weeks for the Isa-Kd group compared to 61 weeks for the Kd group.

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Before receiving SARCLISA, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems, if your healthcare provider prescribes SARCLISA in combination with carfilzomib and dexamethasone for you.
- are pregnant or plan to become pregnant. SARCLISA may harm your unborn baby. You should not receive SARCLISA during pregnancy.
  - Females who are able to become pregnant should use an effective method of birth control during treatment and for 5 months after your last dose of SARCLISA. Talk to your healthcare provider about birth control methods that you can use during this time.
- are breastfeeding or plan to breastfeed. It is not known if SARCLISA passes into your breast milk. You should not breastfeed during treatment with SARCLISA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines. Especially tell your healthcare provider if you have ever taken a medicine for your heart.

How will I receive SARCLISA?

- SARCLISA will be given to you by your healthcare provider by intravenous (IV) infusion into your vein.
- SARCLISA is given in treatment cycles of 28 days (4 weeks), together with either the medicines pomalidomide and dexamethasone, or carfilzomib and dexamethasone.
  - In cycle 1, SARCLISA is usually given weekly.
  - Starting in cycle 2, SARCLISA is usually given every 2 weeks.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.
- Your healthcare provider will give you medicines before each dose of SARCLISA, to help reduce the risk of infusion reactions (make them less frequent and severe).

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines. Especially tell your healthcare provider if you have ever taken a medicine for your heart.

What are the possible side effects of SARCLISA?

SARCLISA may cause serious side effects including:

- **Infusion reactions.** Infusion reactions are common with SARCLISA and can sometimes be severe or life threatening.
  - Your healthcare provider will prescribe medicines before each infusion of SARCLISA to help decrease your risk for infusion reactions or to help make any infusion reaction less severe. You will be monitored for infusion reactions during each dose of SARCLISA.
  - Your healthcare provider may slow down or stop your infusion, or completely stop treatment with SARCLISA if you have an infusion reaction.

Get medical help right away if you develop any of the following symptoms of infusion reaction during or after an infusion of SARCLISA:

  - shortness of breath, wheezing, or trouble breathing
  - swelling of the face, mouth, throat, or tongue
  - heart palpitations
  - chills
  - nausea or vomiting
  - runny or stuffy nose
  - dizziness, lightheadedness, or fainting
  - headache
  - rash or itching

- **Decreased white blood cell counts.** Decreased white blood cell counts are common with SARCLISA and certain white blood cells can be severely decreased. You may have an increased risk of getting certain infections, such as upper and lower respiratory tract infections, and urinary tract infections.

Your healthcare provider will check your blood cell counts during treatment with SARCLISA. Your healthcare provider may prescribe an antibiotic or antiviral medicine to help prevent infection, or a medicine to help increase your white blood cell counts during treatment with SARCLISA.

Tell your healthcare provider right away if you develop any fever or symptoms of infection during treatment with SARCLISA.

- **Risk of new cancers.** New cancers have happened in people during treatment with SARCLISA. Your healthcare provider will monitor you for new cancers during treatment with SARCLISA.
- **Changes in blood tests.** SARCLISA can affect the results of blood tests to match your blood type. Your healthcare provider will do blood tests to match your blood type before you start treatment with SARCLISA. Tell all of your healthcare providers that you are being treated with SARCLISA before receiving blood transfusions.
- **Heart failure.** Heart failure can happen during treatment with SARCLISA in combination with carfilzomib and dexamethasone. Tell your healthcare provider right away if you develop any of the following symptoms:
  - trouble breathing
  - swelling of your ankles, feet, and legs

The most common side effects of SARCLISA in combination with pomalidomide and dexamethasone include:

- lung infection (pneumonia)
- decreased red blood cell counts (anemia)
- upper respiratory tract infection
- decreased platelet counts (thrombocytopenia)
- diarrhea
- back pain
- decreased red blood cells (anemia)
- decrease platelet count (thrombocytopenia)

The most common side effects of SARCLISA in combination with carfilzomib and dexamethasone include:

- upper respiratory tract infection
- bronchitis
- cough
- back pain
- decreased red blood cells (anemia)
- decrease platelet count (thrombocytopenia)
- trouble sleeping
- nausea
- runny nose
- tightness
- trouble breathing

These are not all the possible side effects of SARCLISA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of SARCLISA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about SARCLISA that is written for health professionals.
What are the ingredients in SARCLISA?

**Active ingredient:** isatuximab-irfc

**Inactive ingredients:** histidine, histidine hydrochloride monohydrate, polysorbate 80, sucrose, and water for injection.


SARCLISA is a registered trademark of Sanofi. ©2021 sanofi-aventis U.S. LLC.

For more information, go to www.sanofi-aventis.us or call 1-800-633-1610.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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