APPROVED FOR USE AS EARLY AS FIRST RELAPSE

SARCLISA®
(isatuximab-irfc)
Injection for IV use | 500 mg/25 mL, 100 mg/5 mL

DOSING AND ADMINISTRATION GUIDE

Indication

- SARCLISA (isatuximab-irfc) is 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.
- SARCLISA is indicated, 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.

Important Safety Information

CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.

Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 99% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes.

Please see Important Safety Information throughout, and accompanying full Prescribing Information.

IKEMA: SARCLISA + Kd

IKEMA Trial: **SARCLISA + Carfilzomib and Dexamethasone (Kd)**

Evaluated in 302 patients in a phase 3, multicenter, multinational, randomized, open-label study[1,2]

Patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy (N=302)

Randomized 3:2

- SARCLISA[a] + Kd[b] (n=179)
- Kd[b] (n=123)

Treatment was administered in 28-day cycles until disease progression or unacceptable toxicity.

[a]SARCLISA 10 mg/kg was administered as an IV infusion weekly in the first cycle and every 2 weeks thereafter.

[b]Carfilzomib was administered as an IV infusion during cycle 1 at a dose of 20 mg/m^2 on days 1 and 2, and at 56 mg/m^2 on days 8, 9, 15, and 16; during subsequent cycles, it was administered at 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16. Dexamethasone (IV on the days of SARCLISA and/or carfilzomib infusions, and orally on the other days) 20 mg was given on days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle.

PRIMARY ENDPOINT: PFS*

Key secondary endpoints: ORR, ≥VGPR, CR, MRD negativity, OS

*PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. An interim analysis was conducted when 65% of the 159 PFS events (ie, 103 events) were observed.[1,2]

CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; IV=intravenous; M-protein=monoclonal protein; MRD=minimal (or measurable) residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; VGPR=very good partial response.

Important Safety Information (cont'd)

Infusion-Related Reactions (cont'd)

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients. To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H_2 antagonists, diphenhydramine or equivalent, and dexamethasone.

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade ≥2 reactions, interrupt SARCLISA infusion and provide appropriate medical management.

ICARIA-MM: SARCLISA + Pd

ICARIA-MM Trial: **SARCLISA + Pomalidomide and Dexamethasone (Pd)**

Evaluated in 307 patients in a phase 3, multicenter, multinational, randomized, open-label study[1]

Patients with relapsed and/or refractory multiple myeloma who received at least 2 prior therapies, including lenalidomide and a PI (N=307)

Randomized 1:1

- SARCLISA[a] + Pd[b] (n=154)
- Pd[b] (n=153)

Treatment was administered in 28-day cycles until disease progression or unacceptable toxicity.

[a]SARCLISA 10 mg/kg was administered as an IV infusion weekly in the first cycle and every 2 weeks thereafter.

[b]Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle.

PRIMARY ENDPOINT: PFS†

Key secondary endpoints: ORR,‡ OS

†PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. Median time to follow-up was 11.6 months.

‡sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria.

Pd=pomalidomide and dexamethasone; PI=proteasome inhibitor; PR=partial response; sCR=stringent complete response.

Important Safety Information (cont'd)

Infusion-Related Reactions (cont'd)

For patients with grade 2 or grade 3 reactions, if symptoms improve to grade ≤1, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) IRR occurs and institute appropriate management.

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Dose and Schedule for SARCLISA

Recommended dose[1]

10 mg/kg
actual body weight administered as an IV infusion in combination with Kd or Pd

250-mL
fixed infusion volume

Treatment is repeated until disease progression or unacceptable toxicity

Infusion time decreases to 75 minutes by the third infusion[1]

Incremental escalation of the infusion rate should be considered only in the absence of IRRs.

FIRST INFUSION

3 hours 20 minutes

SECOND INFUSION

1 hour 53 minutes

THIRD INFUSION ONWARD

75 minutes

Weekly dosing transitions to every other week after the first cycle[1]

Treatment is administered in 28-day cycles

Cycle 1 — ***Cycle 2 and beyond***

Day 1 | Day 8 | Day 15 | Day 22 ▶▶ Day 1 | | Day 15 |

On days where both SARCLISA and carfilzomib are administered, administer dexamethasone first, followed by SARCLISA infusion, then followed by carfilzomib infusion.

For additional dosing instructions for combination agents administered with SARCLISA, refer to the study design descriptions on pages 2 and 3 and the respective manufacturer's Prescribing Information.

See page 17 for information about dose modifications.

Premedication[1]

Administer the following premedications prior to infusion of SARCLISA to reduce the risk and severity of IRRs.

Dexamethasone

20 mg (IV on the days of SARCLISA and/or carfilzomib infusions, and orally on the other days) when administered in combination with SARCLISA and carfilzomib

40 mg orally or IV (or 20 mg orally or IV for patients ≥75 years of age) when administered in combination with SARCLISA and pomalidomide

Acetaminophen

650 mg to 1000 mg orally (or equivalent)

H_2 antagonists

Institution-preferred agent

Diphenhydramine

25 mg to 50 mg orally or IV (or equivalent). The IV route is preferred for at least the first 4 infusions

The above recommended dose of dexamethasone (orally or IV) corresponds to the total dose to be administered only once before infusion as part of the premedication and of the backbone treatment, before SARCLISA and carfilzomib or SARCLISA and pomalidomide administration.

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

NO POST-INFUSION MEDICATIONS
are required for SARCLISA

Important Safety Information (cont'd)

Neutropenia
SARCLISA may cause 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. The most frequent neutropenic infections included infections of the upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

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IRR=infusion-related reaction.

Preparation and Administration

Prepare the solution for infusion using an aseptic technique[1]

Calculate the dose (mg) of required SARCLISA based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly)

– More than one vial of SARCLISA 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, diluent bag that is equal to the required volume of SARCLISA injection

Withdraw the necessary volume of SARCLISA injection and dilute by adding to the infusion bag of 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, to achieve the appropriate concentration of SARCLISA for infusion

The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP), or ethyl vinyl acetate (EVA)

Gently homogenize the diluted solution by inverting the bag. Do not shake

Important Safety Information (cont'd)

Neutropenia (cont'd)
In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3-4 neutropenia in 19% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%).

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 SARCLISA 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 SARCLISA are recommended.

Preparation and Administration (cont'd)

Example dose calculations[1]

Dose **x** patient weight	Required dose	Withdrawal amount (20 mg/mL)
10 mg/kg × 60 kg	**600 mg** (500 mg, 100 mg)	**30 mL**
10 mg/kg × 80 kg	**800 mg** (500 mg, 100 mg, 100 mg, 100 mg)	**40 mL**
10 mg/kg × 100 kg	**1000 mg** (500 mg, 500 mg)	**50 mL**

Administering SARCLISA[1]

- Administer the infusion solution by IV infusion using an IV tubing infusion set (in PE, PVC with or without DEHP, polybutadiene [PBD], or polyurethane [PU]) with a 0.22-micron in-line filter (polyethersulfone [PES], polysulfone, or nylon)
- The infusion solution should be administered for a period of time that will depend on the infusion rate (see table on page 8)
- Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 36°F to 46°F (2°C to 8°C), followed by 8 hours (including the infusion time) at room temperature
- Do not administer SARCLISA infusion solution concomitantly in the same IV line with other agents
- On days where both SARCLISA and carfilzomib are administered, administer dexamethasone first, followed by SARCLISA infusion, then followed by carfilzomib infusion

Important Safety Information (cont'd)

Second Primary Malignancies
The incidence of second primary malignancies is increased in patients treated with SARCLISA-containing regimens. The overall incidence of second primary malignancies in all the SARCLISA-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 IKEMA, second primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm.

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Infusion Rates of SARCLISA Administration[1]

Incremental escalation of the infusion rate should be considered only in the absence of IRRs. Refer to page 17 for dose modifications.

	Dilution volume	Initial rate	Absence of IRR	Rate increment	Maximum rate	Total time (if no rate adjustments)
First infusion	**250 mL**	**25 mL/h**	**60 min**	25 mL/h every 30 min	150 mL/h	**3 h 20 min**
Second infusion	**250 mL**	**50 mL/h**	**30 min**	50 mL/h for 30 min, then increase by 100 mL/h	200 mL/h	**1 h 53 min**
Subsequent infusions	**250 mL**	**200 mL/h**	**–**	–	200 mL/h	**75 min**

SARCLISA should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage IRRs if they occur.

75-MINUTE INFUSION TIME

starting after the second infusion in the absence of IRRs

Important Safety Information (cont'd)

Second Primary Malignancies (cont'd)

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

Monitor patients for the development of second primary malignancies.

Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false-positive indirect antiglobulin test (indirect Coombs test). The indirect antiglobulin test was positive during Isa-Pd treatment in 68% of the tested patients, and during Isa-Kd treatment in 63% of patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment.

Infusion Times With Rate Increments[1]

Incremental escalation of the infusion rate should be considered only in the absence of IRRs. Refer to page 17 for dose modifications.

SARCLISA week 1 infusion, single dose			250-mL dilution volume	
Start	End	Rate (mL/h)	mL infused	Total infused
0:00	0:30	25	12.5	12.5
0:30	1:00	25	12.5	25
1:00	1:30	50	25	50
1:30	2:00	75	37.5	87.5
2:00	2:30	100	50	137.5
2:30	3:00	125	62.5	200
3:00	3:20	150	50	250
Total time	**3:20**			

SARCLISA week 2 infusion, single dose			250-mL dilution volume	
Start	End	Rate (mL/h)	mL infused	Total infused
0:00	0:30	50	25	25
0:30	1:00	100	50	75
1:00	1:52:30	200	175	250
Total time	**1:52:30**			

SARCLISA week 3 infusion, single dose			250-mL dilution volume	
Start	End	Rate (mL/h)	mL infused	Total infused
0:00	1:15	200	250	250
Total time	**1:15**			

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Adverse Reactions for SARCLISA + Kd

Adverse reactions (≥10%) in patients receiving SARCLISA + Kd with a difference between arms of ≥5% compared with Kd alone[1]

	SARCLISA + Kd (n=177)			Kd (n=122)		
Adverse reactions	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
General disorders and administration site conditions						
IRR[a]	46%	0.6%	0%	3.3%	0%	0%
Infections						
Upper respiratory tract infection[b]	67%	9%	0%	57%	7%	0%
Pneumonia[c]	36%	19%	3.4%	30%	15%	2.5%
Bronchitis[d]	24%	2.3%	0%	13%	0.8%	0%
Vascular disorders						
Hypertension[e]	37%	20%	0.6%	32%	18%	1.6%
Respiratory, thoracic, and mediastinal disorders						
Dyspnea[f]	29%	5%	0%	24%	0.8%	0%
Cough[g]	23%	0%	0%	15%	0%	0%
Gastrointestinal disorders						
Diarrhea	36%	2.8%	0%	29%	2.5%	0%
Vomiting	15%	1.1%	0%	9%	0.8%	0%
General disorders and administration site conditions						
Fatigue[h]	42%	5%	0%	32%	3.3%	0%

[a]IRR includes IRR, cytokine release syndrome, and hypersensitivity.
[b]Upper respiratory tract infection includes acute sinusitis, chronic sinusitis, H1N1 influenza, H3N2 influenza, influenza, laryngitis, laryngitis viral, nasal herpes, nasopharyngitis, pharyngitis, pharyngotonsillitis, respiratory syncytial virus infection, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, tracheitis, upper respiratory tract infection, viral rhinitis, respiratory tract infection, respiratory tract infection viral, influenza-like illness, parainfluenzae virus infection, respiratory tract infection bacterial, and viral upper respiratory tract infection.
[c]Pneumonia includes atypical pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, *Pneumocystis jirovecii* pneumonia, pneumonia, pneumonia influenzal, pneumonia legionella, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, pulmonary sepsis, and pulmonary tuberculosis.
[d]Bronchitis includes bronchitis, bronchitis viral, respiratory syncytial virus bronchitis, bronchitis chronic, and tracheobronchitis.
[e]Hypertension includes hypertension, blood pressure increased, and hypertensive crisis.
[f]Dyspnea includes dyspnea and dyspnea exertional.
[g]Cough includes cough, productive cough, and allergic cough.
[h]Fatigue includes fatigue and asthenia.

IKEMA: SARCLISA + Kd

Additional Safety Experience for SARCLISA + Kd

Hematology laboratory abnormalities in patients receiving SARCLISA + Kd vs Kd alone[1]

	SARCLISA + Kd (n=177)			Kd (n=122)		
Laboratory parameter	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hemoglobin decreased	99%	22%	0%	99%	20%	0%
Lymphocytes decreased	94%	52%	17%	95%	43%	14%
Platelets decreased	94%	19%	11%	88%	16%	8%
Neutrophils decreased	55%	18%	1.7%	43%	7%	0.8%

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

Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. In case of infection, appropriate standard therapy should be instituted. Antibiotics and antiviral prophylaxis can be considered during treatment.

Serious adverse reactions[1,2]

- Serious adverse reactions occurred in 59% of patients receiving SARCLISA + Kd
  - The most frequent serious adverse reactions in >5% of patients who received SARCLISA + Kd were pneumonia (25%) and upper respiratory tract infections (9%)
- Fatal adverse reactions occurred in 3.4% of patients receiving SARCLISA + Kd (those occurring in >1% of patients were pneumonia in 1.7% and cardiac failure in 1.1% of patients) vs 3.3% in the Kd arm

Permanent treatment discontinuation due to adverse reactions (grades 1 to 4)[1,2]

SARCLISA + Kd	Kd
8%	14%

- The most frequent adverse reactions requiring permanent discontinuation were infections (2.8%, SARCLISA + Kd; 4.9%, Kd)
- Dosage interruptions due to an adverse reaction occurred in 33% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was IRR (30%)

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Adverse Reactions for SARCLISA + Pd

Adverse reactions (≥10%) in patients receiving SARCLISA + Pd with a difference between arms of ≥5% compared with Pd alone[1]

	SARCLISA + Pd (n=152)			Pd (n=149)		
Adverse reactions	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
General disorders and administration site conditions						
IRR[a]	38%	1.3%	1.3%	0%	0%	0%
Infections						
Upper respiratory tract infection[b]	57%	9%	0%	42%	3.4%	0%
Pneumonia[c]	31%	22%	3.3%	23%	16%	2.7%
Blood and lymphatic system disorders						
Febrile neutropenia	12%	11%	1.3%	2%	1.3%	0.7%
Respiratory, thoracic, and mediastinal disorders						
Dyspnea[d]	17%	5%	0%	12%	1.3%	0%
Gastrointestinal disorders						
Diarrhea	26%	2%	0%	19%	0.7%	0%
Nausea	15%	0%	0%	9%	0%	0%
Vomiting	12%	1.3%	0%	3.4%	0%	0%

[a]IRR includes IRR, cytokine release syndrome, and drug hypersensitivity.
[b]Upper respiratory tract infection includes bronchiolitis, bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, nasopharyngitis, parainfluenzae virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
[c]Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenzal, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and *Pneumocystis jirovecii* pneumonia.
[d]Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

Important Safety Information (cont'd)

Laboratory Test Interference (cont'd)
Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and that SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.

Please see Important Safety Information throughout, and accompanying full Prescribing Information.

Additional Safety Experience for SARCLISA + Pd

Hematology laboratory abnormalities in patients receiving SARCLISA + Pd vs Pd alone[1]

	SARCLISA + Pd (n=152)			Pd (n=149)		
Laboratory parameter	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hemoglobin decreased	99%	32%	0%	97%	28%	0%
Neutrophils decreased	96%	24%	61%	92%	38%	31%
Lymphocytes decreased	92%	42%	13%	92%	35%	8%
Platelets decreased	84%	14%	16%	79%	9%	15%

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

Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. In case of infection, appropriate standard therapy should be instituted. Antibiotics and antiviral prophylaxis can be considered during treatment.

Serious adverse reactions[1,2]

- Serious adverse reactions occurred in 62% of patients receiving SARCLISA + Pd
  - Serious adverse reactions in >5% of patients who received SARCLISA + Pd included pneumonia (26%), upper respiratory tract infection (7%), and febrile neutropenia (7%)
- Fatal adverse reactions occurred in 11% of patients in the SARCLISA + Pd arm (those that occurred in >1% of patients were pneumonia and other infections [3%]) vs 11% in the Pd arm

Permanent treatment discontinuation due to adverse reactions (grades 1 to 4)[1,2]

SARCLISA + Pd	Pd
7%	12%

- Dosage interruptions due to an adverse reaction occurred in 31% of patients who received SARCLISA + Pd
  - Discontinuations from treatment due to infection were reported in 2.6% of patients receiving SARCLISA + Pd vs 5.4% of patients receiving Pd alone
  - The most frequent adverse reaction requiring dosage interruption was IRR (28%)

THE ADDITION OF SARCLISA TO Pd
did not increase treatment discontinuations due to adverse reactions vs Pd alone[1,2]

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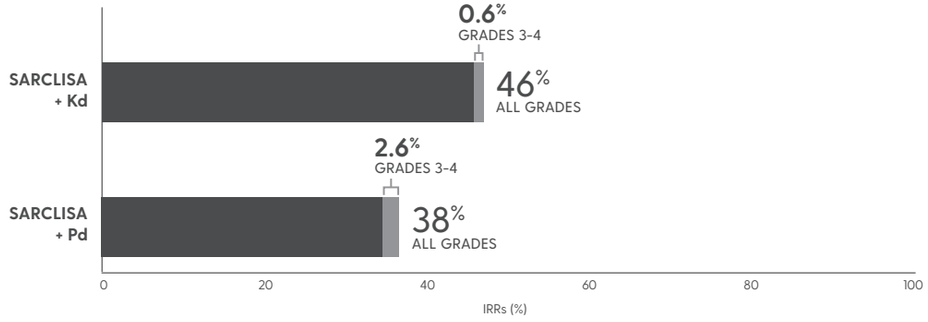
Additional Safety Experience With SARCLISA

IRRs[1]

IRRs were observed in 46% and 38% of patients in the IKEMA and ICARIA-MM trials, respectively.

IRRs in patients receiving SARCLISA + Kd and SARCLISA + Pd



Timing of IRRs

In ICARIA-MM, all IRRs started during the first infusion of SARCLISA. In IKEMA, IRRs occurred on the infusion day in 99% of episodes, and 95% of patients receiving SARCLISA + Kd who experienced an IRR did so during the first cycle of treatment

All IRRs resolved on the same day in 98% of cases in the ICARIA-MM trial and in 74% of cases in the IKEMA trial

Symptoms of IRRs

The most common symptoms (≥5%) of an IRR in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea

– Anaphylactic reactions occurred in <1% of patients

Serious IRRs, including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms included cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling

Dosage interruption and discontinuation due to IRRs

Dosage interruption of SARCLISA due to IRRs occurred in 30% and 28% of patients in the IKEMA and ICARIA-MM trials, respectively

SARCLISA alone was discontinued in 3% of patients in the ICARIA-MM trial and in 0.6% of patients in the IKEMA trial due to IRRs

Additional Safety Experience With SARCLISA (cont'd)

Managing IRRs[1,3]

- To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H_2 antagonists, diphenhydramine or equivalent, and dexamethasone
- Monitor vital signs frequently during the entire SARCLISA infusion

Grade 1 IRRs	No interruption or intervention is indicated.	
Grade 2-3 IRRs	Interrupt SARCLISA infusion and provide appropriate medical management.	**If symptoms improve to grade ≤1,** restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. • If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in the infusion rate table on page 8 **If symptoms do not improve to grade ≤1** after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management.
Grade 4 IRRs	Permanently discontinue SARCLISA and institute appropriate management.	

Defining IRR grades[3]

Grade 1	Mild transient reaction.
Grade 2	Therapy or infusion interruption indicated, but IRR responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.
Grade 3	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.
Grade 4	Life-threatening consequences; urgent intervention indicated.

NSAID=nonsteroidal anti-inflammatory drug.

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Additional Safety Experience With SARCLISA (cont'd)

Infections[1]

- The incidence of grade 3 or higher infections was 43% in the SARCLISA + Pd group in the ICARIA-MM trial and 38% in the SARCLISA + Kd group in the IKEMA trial
- Pneumonia was the most commonly reported severe infection across both trials, with grade 3 reported in 22% of patients in the SARCLISA + Pd group compared with 16% in the Pd group, and in 19% of patients in the SARCLISA + Kd group compared with 15% in the Kd group. Grade 4 was reported in 3.3% of patients in the SARCLISA + Pd group compared with 2.7% in the Pd group, and in 3.4% of patients in the SARCLISA + Kd group compared with 2.5% in the Kd group
- Discontinuations from treatment due to infection were reported in 2.6% of patients in the SARCLISA + Pd group compared with 5.4% in the Pd group, and in 2.8% of patients in the SARCLISA + Kd group compared with 4.9% in the Kd group
- Fatal infections were reported in 3.3% of patients in the SARCLISA + Pd group compared with 4% in the Pd group, and in 2.3% of patients in the SARCLISA + Kd group compared with 0.8% in the Kd group

Neutropenia[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
- If grade 4 neutropenia occurs, consider dose delays until neutrophil count recovery to at least 1.0 × 10^9/L, and provide supportive care with growth factors, according to institutional guidelines

Cardiac failure in the IKEMA trial[1*+]

- In IKEMA, cardiac failure was reported in 7.3% of patients in the SARCLISA + Kd group (grade ≥3, 4%) and in 6.6% of patients in the Kd group (grade ≥3, 4.1%)
- In IKEMA, serious cardiac failure was observed in 4% of patients in the SARCLISA + Kd group and in 3.3% of patients in the Kd group

*Cardiac failure included cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure, and pulmonary edema.
+See the current Prescribing Information for carfilzomib for more information.

Additional Safety Experience With SARCLISA (cont'd)

Second primary malignancies[1]

- Monitor patients for the development of second primary malignancies
- The incidence of second primary malignancies is increased in patients treated with regimens that contain SARCLISA
  - The overall incidence of second primary malignancies in all SARCLISA-exposed patients was 3.6%
  - In ICARIA-MM, second primary malignancies occurred in 3.9% of patients in the SARCLISA + Pd arm and in 0.7% of patients in the Pd arm
  - In IKEMA, second primary malignancies occurred in 7% of patients in the SARCLISA + 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 regimens that contain SARCLISA and 1.5% with comparative regimens) and solid tumors other than skin cancer (1.8% with regimens that contain SARCLISA and 1.5% with comparative regimens). All patients with skin cancer continued treatment after resection of the skin cancer

Dose modifications[1]

Dose delay may be required to allow for recovery of blood counts in the event of hematological toxicity. For dosing instructions for combination agents administered with SARCLISA, refer to the study design descriptions on pages 2 and 3 and the respective manufacturer's Prescribing Information.

***NO DOSE REDUCTION** of SARCLISA is recommended*

Please see Important Safety Information throughout, and accompanying full Prescribing Information.

SARCLISA® (isatuximab-irfc)
Injection for IV use | 500 mg/25 mL, 100 mg/5 mL

Storage and Handling

SARCLISA injection is a clear to slightly opalescent, colorless to slightly yellow solution, essentially free of visible particulates, supplied as follows[1]:

- One 100 mg/5 mL single-dose vial in a carton: NDC 0024-0654-01
- One 500 mg/25 mL single-dose vial in a carton: NDC 0024-0656-01

Storage requirements[1]

- Store SARCLISA 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

Handling and disposal[1]

Discard unused portion of solution. All materials that have been utilized for dilution and administration should be disposed of according to standard procedures.

Important Safety Information (cont'd)

Laboratory Test Interference (cont'd)

Interference with Serum Protein Electrophoresis and Immunofixation Tests

SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Important Safety Information (cont'd)

Embryo-Fetal Toxicity

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

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 (≥80%) were decreased hemoglobin, decreased neutrophils, decreased lymphocytes, and decreased platelets.

In combination with carfilzomib and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain. The most common hematology laboratory abnormalities (≥80%) were decreased hemoglobin, decreased lymphocytes, and decreased platelets.

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%]).

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in >5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients).

USE IN SPECIAL POPULATIONS

Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see Important Safety Information throughout, and accompanying full Prescribing Information.

References: 1. SARCLISA [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. **2.** Data on file. sanofi-aventis U.S. LLC. **3.** US Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE)* v4.03. Bethesda, MD: National Cancer Institute; 2010.

SARCLISA®
(isatuximab-irfc)
Injection for IV use | 500 mg/25 mL, 100 mg/5 mL

Key Benefits of SARCLISA Dosing and Administration

75-minute infusion time starting after the second infusion in the absence of IRRs[1]

- SARCLISA alone was discontinued in 3% of patients in the ICARIA-MM trial and in 0.6% of patients in the IKEMA trial due to IRRs

Weight-based dosing with 250-mL fixed-volume dilution[1]

- Vials are available in convenient 100 mg/5 mL and 500 mg/25 mL sizes

No post-infusion medications required[1]

- Premedication is administered prior to infusion to reduce the risk and severity of IRRs

CareASSIST BY SANOFI GENZYME FOR SARCLISA

Resources and support for your eligible patients

Call **1-833-WE+CARE** (1-833-930-2273), Mon – Fri, 9 AM – 8 PM ET,
or visit **SanofiCareAssist.com/hcp/sarclisa** to learn more

Indication

- SARCLISA (isatuximab-irfc) is 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.
- SARCLISA is indicated, 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.

Important Safety Information

CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.

Please see Important Safety Information throughout, and accompanying full Prescribing Information.

SANOFI GENZYME

SARCLISA®
(isatuximab-irfc)
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