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

For your adult patients with relapsed or refractory multiple myeloma

# SARCLISA IN COMBINATION WITH Kd OR Pd[1]

NCCN
CATEGORY 1 PREFERRED

**National Comprehensive Cancer Network® (NCCN®) recommends isatuximab-irfc (SARCLISA) in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma as a Category 1 Preferred option in combination with carfilzomib and dexamethasone or with pomalidomide and dexamethasone[2]:**

- ✓ **For early relapses (1-3 prior therapies)***
- ✓ **Option for patients refractory to either lenalidomide or bortezomib**

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. Recommendation for isatuximab-irfc (SARCLISA) in combination with carfilzomib and dexamethasone based on results of interim analysis.
*After 2 prior therapies including lenalidomide and a proteasome inhibitor for isatuximab-irfc in combination with pomalidomide and dexamethasone.
NCCN=National Comprehensive Cancer Network® (NCCN®).

| **Superior PFS vs Kd at interim analysis** (median follow-up of 20.7 months)[1] | **SARCLISA + Kd: mPFS NR** Kd: mPFS 20.27 months[1] | HR=0.548 (95% CI: 0.37, 0.82; *P*=0.0032)[1] |
|---|---|---|

## *At a median follow-up of 44 months, SARCLISA + Kd doubled mPFS vs Kd alone[3]*

| **~42 months mPFS with SARCLISA + Kd** | IKEMA final analysis: mPFS 41.7 months with SARCLISA + Kd vs 20.8 months with Kd alone, **HR=0.59** (95% CI: 0.42, 0.83) |
|---|---|

**Discontinuation due to adverse reactions at interim analysis: 8% with SARCLISA + Kd vs 14% with Kd alone[1,4]**

**Discontinuation due to adverse reactions at final analysis: 12.4% with SARCLISA + Kd (n=177) vs 18.0% with Kd alone (n=122)[3]**

PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using IMWG criteria. A preplanned interim analysis was conducted when 65% of 159 PFS events were observed, with a median follow-up of 20.7 months. *P* value is not reported as this is a non-inferential analysis of the primary endpoint that was met at the time of the interim analysis.[1,4]

**Final analysis:** A prespecified final analysis was conducted when 159 PFS events were observed, with a median follow-up of 44 months. This analysis follows censoring applied to the IKEMA PFS data in the Prescribing Information. Censoring per the original statistical plan resulted in a mPFS of 35.7 months with SARCLISA + Kd (95% CI: 25.8, 44.0) vs 19.2 months with Kd alone (95% CI: 15.8, 25.0), HR=0.58 (95% CI: 0.42, 0.79).[3]

**IKEMA study design:** IKEMA, a multicenter, multinational, randomized, open-label, 2-arm, phase 3 study, evaluated the efficacy and safety of SARCLISA in 302 patients with RRMM who had received 1 to 3 prior therapies. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Kd (n=179) or Kd alone (n=123), administered in 28-day cycles until disease progression or unacceptable toxicity. PFS was the primary endpoint; ORR, ≥VGPR, CR, MRD-, and OS were key secondary endpoints.[1,4]

## *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
- 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

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

## *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.

## *Important Safety Information (cont'd)*

**Infusion-Related Reactions (cont'd)**
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.

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. 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.

**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%).

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.

**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.

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.

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## *Important Safety Information (cont'd)*

**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.

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.

***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.

**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 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.

CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; IV=intravenous; Kd=carfilzomib and dexamethasone; M-protein=monoclonal protein; mPFS=median progression-free survival; MRD-=minimal (or measurable) residual disease negative/negativity; NR=not reached; ORR=overall response rate; OS=overall survival; Pd=pomalidomide and dexamethasone; PFS=progression-free survival; PR=partial response; RRMM=relapsed or refractory multiple myeloma; sCR=stringent complete response; VGPR=very good partial response.

**References: 1.** SARCLISA [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.3.2023. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed December 19, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. **3.** Moreau P, Dimopoulos M-A, Mikhael J, et al; IKEMA study group. Updated progression-free survival and depth of response in IKEMA, a randomized phase 3 trial of isatuximab, carfilzomib and dexamethasone (Isa-Kd) vs Kd in relapsed multiple myeloma. Presented at: the 8th World Congress on Controversies in Multiple Myeloma (COMy); May 12-15, 2022; Paris, France. **4.** Data on file. sanofi-aventis U.S. LLC.

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## *SARCLISA + Pd extended mPFS to ~1 year[1]*

**11.53 months mPFS with SARCLISA + Pd**

ICARIA-MM:
mPFS: 11.53 months with SARCLISA + Pd (n=154) vs 6.47 months with Pd alone (n=153), **HR=0.596** (95% CI: 0.44, 0.81; *P*=0.0010)

**Discontinuation due to adverse reactions: 7% with SARCLISA + Pd vs 12% with Pd alone[1,4]**

**ICARIA-MM study design:** ICARIA-MM, a multicenter, open-label, randomized, phase 3 study, evaluated the efficacy and safety of SARCLISA in 307 patients with RRMM who had received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. PFS was the primary endpoint⁺; ORR and OS were key secondary endpoints.[1‡]

⁺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.[1]
‡sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria.[1]

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## *Indication*

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