Prescribing Information: SARCLISA (isatuximab) 20 mg/mL concentrate for solution for infusion

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentations: Each vial contains 100 mg of isatuximab in 5 mL of concentrate or contains 500 mg of isatuximab in 25 mL of concentrate.

Indication: SARCLISA is indicated: (1) in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy (2) in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Dosage and Administration: SARCLISA should be administered intravenously (IV) by a healthcare professional, in an environment where resuscitation facilities are available. Pre-medication: Pre-medication with the following medicinal products, should be administered 15 – 60 minutes prior to starting a SARCLISA infusion for the prevention of infusion reaction (IR): Dexamethasone 40 mg oral or IV (or 20 mg oral or IV for patients ≥75 years of age) when administered in combination with isatuximab and pomalidomide; Dexamethasone 20 mg (intravenous on the days of isatuximab infusion, and oral on the other days): when administered in combination with isatuximab, bortezomib, and lenalidomide. Paracetamol 650 mg to 1000 mg oral (or equivalent); H2 antagonists (ranitidine 50 mg IV or equivalent [e.g. cimetidine]), or oral proton pump inhibitors (e.g. omeprazole, esomeprazole). Diphenhydramine 25 mg to 50 mg IV or oral (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]) – IV use is preferred for at least the first 4 infusions. The above recommended dose of dexamethasone (oral or IV) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide, and before isatuximab, bortezomib and lenalidomide administration. Patients who do not experience an IR upon their first 4 administrations of SARCLISA may have their need for subsequent premedication reconsidered. Management of neutropenia: The use of colony-stimulating factors (e.g. G-CSF) should be considered to mitigate the risk of neutropenia. In the event of Grade 3 or 4 neutropenia, or febrile neutropenia and/or neutropenic infection, SARCLISA administration should be delayed or omitted until recovery. Prevention of infection: Antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) according to treatment guidelines should be considered during treatment. Posology: The recommended dose of SARCLISA is 10 mg/kg body weight administered as an IV infusion. If administered in combination with pomalidomide and dexamethasone (Isa-Pd regimen) each treatment cycle consists of a 28-day period. *Cycle 1 (28-day cycle):* Dosing on days 1, 8, 15 and 22 (weekly). *Cycle 2 and beyond (28-day cycle):* Dosing on days 1, 15 (every 2 weeks). If administered in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd regimen) each treatment cycle consists of a 42-day period from cycle 1 to 4, and a 28-day period from cycle 5. *Cycle 1 (42-day cycle):* Dosing on days 1, 8, 15, 22 and 29. *Cycles 2 to 4 (42-day cycles):* Dosing on days 1, 15 and 29 (every 2 weeks). *Cycle 5 to 17 (28-day cycles):* Dosing on days 1 and 15 (every 2 weeks). *Cycle 18 and beyond (28-day cycle):* Dosing on day 1 (every 4 weeks). Treatment is repeated until disease progression or unacceptable toxicity. For other medicinal products that are administered with SARCLISA, refer to the respective current SmPC. The administration schedule must be carefully followed. Missed dose: 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. Dose adjustments: No dose reduction of SARCLISA is recommended. Administration adjustments should be made if patients experience IRs or in case of Grade 3 or 4 neutropenia, or febrile neutropenia and/or neutropenic infection. Please refer to the SmPC for full details on infusion rates and administration adjustments.

Special Populations: Elderly patients, patients with renal impairment (including end-stage renal disease) and patients with hepatic impairment: no dose adjustment is recommended. (Data in patients with moderate and severe hepatic impairment are limited, but there is no evidence to suggest that dose adjustment is required in these patients). Paediatric population (<18 years old): Outside its authorised indications, SARCLISA has been studied in children aged 28 days to less than 18 years of age with relapsed or refractory acute lymphoblastic or myeloid leukaemia but efficacy has not been established.

Contraindications: Hypersensitivity to the active substance or to any of its excipients.

Warnings and Precautions: Infusion reactions (IRs): IRs, mostly mild or moderate, have been observed in 38.2% of patients treated with SARCLISA in ICARIA-MM (Isa-Pd regimen), and in 24.0% of patients treated with Isa-VRd in IMROZ. In ICARIA-MM, all IRs started during the first SARCLISA infusion and resolved on the same day in 98% of the infusions. The most common symptoms of included dyspnoea, cough, chills and nausea and the most common severe signs and symptoms included hypertension, dyspnoea and bronchospasm. In IMROZ, the IRs started on the infusion day in all patients, mostly during the first SARCLISA infusion, and resolved the same day in 97.3% of patients. All IRs resolved. The most common symptoms included dyspnoea and chills and the most common severe sign and symptom was hypertension. Serious IRs including severe anaphylactic reactions have been observed after SARCLISA administration. To decrease the risk and severity of IRs, patients should be appropriately pre-medicated prior to SARCLISA infusion and vital signs should be frequently monitored during the entire infusion. When required, interrupt SARCLISA infusion and provide appropriate medical and supportive measures. In case symptoms do not improve to Grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate treatment with medicinal products, require hospitalization or are life-threatening, permanently discontinue SARCLISA and institute appropriate management. Neutropenia: In patients receiving Isa-Pd, neutropenia was reported as a laboratory abnormality in 96.1% of patients and as an adverse reaction in 46.7% of patients, with Grade 3 – 4 neutropenia reported as a laboratory abnormality in 84.9% of patients and as an adverse reaction in 45.4% of patients. Neutropenic complications have been observed in 30.3% of patients, including 11.8% of febrile neutropenia and 25.0% of neutropenic infections. In patients treated with Isa-VRd, neutropenia was reported as a laboratory abnormality in 87.5% of patients and as an adverse reaction in 30% of patients, with Grade 3 – 4 neutropenia reported as a laboratory abnormality in 54.4% of patients (with 35.7% Grade 3 and 18.6% Grade 4) and as an adverse reaction in 30% of patients. Neutropenic complications have been observed in 12.5% of patients, including 2.3% of febrile neutropenia and 10.6% of neutropenic infection. Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. Infection: A higher incidence of infections including Grade ≥3 infections, mainly pneumonia, upper respiratory tract infection and bronchitis, occurred with SARCLISA. Patients receiving SARCLISA should be closely monitored for signs of infection and appropriate standard therapy instituted (including antibiotics and antiviral prophylaxis). Second primary malignancies (SPMs): In ICARIA-MM, SPMs were reported at a median follow-up time of 52.44 months in 10 patients (6.6%) treated with Isa-Pd and in 3 patients (2%) treated with Pd. SPM

were skin cancer in 6 patients treated with Isa-Pd and in 3 patients treated with Pd, solid tumours other than skin cancer in 3 patients treated with Isa-Pd (one patient also had a skin cancer), and haematological malignancy (myelodysplastic syndrome) in 1 patient treated with Isa-Pd. Patients continued treatment after resection of the new malignancy, except two patients treated with Isa-Pd. One patient developed metastatic melanoma and the other developed myelodysplastic syndrome. In IMROZ study, at a median follow-up time of 59.73 months, SPMs were reported in 42 patients (16.0%) treated with Isa-VRd (0.041 events per patient-year) and in 16 patients (8.8%) treated with VRd (0.026 events per patient-year). SPMs were skin cancers in 22 patients (8.4%) treated with Isa-VRd and in 7 patients (3.9%) treated with VRd, were solid tumours other than skin cancer in 17 patients (6.5%) treated with Isa-VRd and in 7 patients (3.9%) treated with VRd, and haematological malignancy in 3 patients (1.1%) treated with Isa-VRd and in 2 patients (1.1%) treated with VRd. Patients with SPM of skin cancer continued treatment after resection of the skin cancer, except one patient in each treatment group. SPMs with fatal outcome were reported in 6 patients (2.3%) treated with Isa-VRd (neuroendocrine carcinoma of the skin, malignant melanoma, squamous cell carcinoma of skin, squamous cell carcinoma of lung, colorectal cancer, and rectal adenocarcinoma) and in 2 patients (1.1%) treated with VRd (metastases to peritoneum and adenocarcinoma of colon). The overall incidence of SPMs in all the SARCLISA-exposed patients is 6.0%. Physicians should carefully evaluate patients before and during treatment as per IMWG guidelines for occurrence of SPM and initiate treatment as indicated. Tumour lysis syndrome (TLS): Cases of TLS have been reported in patients who received isatuximab. Patients should be monitored closely and appropriate precautions taken.

Interactions: Interference with serological testing: Because CD38 protein is expressed on the surface of red blood cells, SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests where interference may persist for at least 6 months after the last SARCLISA infusion), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with SARCLISA. To avoid potential problems with Red Blood Cell transfusion, patients being treated with SARCLISA should have blood type and screen tests performed prior to the first SARCLISA infusion. Phenotyping may be considered prior to starting SARCLISA treatment as per local practice. If treatment with SARCLISA has already started, the blood bank should be informed that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol (DTT)-treated RBCs. Patients should be monitored for theoretical risk of haemolysis. 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 (SPE) and immunofixation (IFE) tests: SARCLISA may be detected on SPE and IFE assays used for monitoring disease monoclonal immunoglobins (M-protein), and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria including the determination of complete response in some patients with IgG kappa myeloma protein. In patients with persistent very good partial response, where isatuximab interference is suspected, consider using a validated isatuximab-specific IFE assay to distinguish isatuximab from any remaining endogenous M-protein in the patient's serum, to facilitate determination of a complete response.

Fertility, pregnancy and lactation: Women of childbearing potential treated with SARCLISA should use effective contraception during treatment and for at least 5 months after cessation of treatment. There are no available data on isatuximab use in pregnant women. Immunoglobulin G1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. The use of SARCLISA in pregnant women is not recommended. It is unknown whether isatuximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; however, a risk to the breast-fed infant cannot be excluded during this short period just after birth. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from isatuximab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No human and animal data are available to determine potential effects of isatuximab on fertility in males and females.

Adverse Reactions: ***Isa-Pd:*** Very common: pneumonia*, upper respiratory tract infection, bronchitis, neutropenia, thrombocytopenia, decreased appetite, dyspnoea, diarrhoea, nausea, vomiting, infusion reaction. Common: Herpes zoster, skin cancer, solid tumour (non-skin cancer), febrile neutropenia*, anaemia, atrial fibrillation, weight decreased. Other Serious Adverse Drug Reactions (Uncommon): haematology malignancy and anaphylactic reaction. ***Isa-VRd:*** Very Common: pneumonia*, bronchitis, Covid-19*, neutropenia, thrombocytopenia, cataract, diarrhoea, fatigue, infusion reaction, peripheral sensory neuropathy, constipation, upper respiratory tract infection, oedema peripheral, insomnia, back pain, asthenia. Common: skin cancer, solid tumour (non-skin cancer), anaemia, vomiting. Other Serious Adverse Drug Reactions (Uncommon): haematology malignancy and anaphylactic reaction. *These adverse events also occurred as serious adverse events. *Prescribers should consult the SmPC in relation to other adverse reactions.*

Legal Category: POM

List price: SARCLISA 100 mg x 1 vial: £506.94; SARCLISA 500 mg x 1 vial: £2,534.69.

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Marketing Authorisation Holder: Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to the Sanofi drug safety department on Tel: 0800 0902 314. Alternatively, send via email to UK-drugsafety@sanofi.com