▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – SARCLISA® (ISATUXIMAB)

1 NAME OF THE MEDICINE

Sarclisa (isatuximab) 20mg/mL concentrated injection for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of Sarclisa concentrated injection contains 20mg isatuximab. Each single-use vial of Sarclisa concentrated injection contains 100mg or 500mg isatuximab.

Isatuximab is an immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to a specific extracellular epitope of cluster of differentiation 38 (CD38) receptor and triggers several mechanisms leading to the death of CD38 expressing tumor cells.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrated injection for infusion.

Sarclisa is a colourless to slightly yellow solution, essentially free of visible particulates, containing no antimicrobial preservatives.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Sarclisa is indicated in combination with pomalidomide and dexamethasone, for the treatment of patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI).

4.2 DOSE AND METHOD OF ADMINISTRATION

Sarclisa should be administered by a healthcare professional, in an environment where resuscitation facilities are available.

Premedication

Premedication should be used prior to each Sarclisa infusion with the following medications to reduce the risk and severity of infusion reactions (IRs):

- Dexamethasone 40 mg administered orally or intravenously or 20 mg administered orally or intravenously for patients ≥75 years of age.
- Paracetamol 500 mg to 1000 mg (or equivalent) administered orally.
- 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 (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]) administered intravenously or orally. Intravenous route is preferred for at least the first 4 infusions.

Above recommended dose of dexamethasone (administered orally or intravenously) 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 administration.

The recommended premedication agents should be administered 15-60 minutes prior to starting a Sarclisa infusion. Patients who do not experience an IR upon their first 4 administrations of Sarclisa may have their need for subsequent premedication reconsidered.

Dose

The recommended dose of SARCLISA is 10 mg/kg body weight administered as an intravenous infusion (IV) in combination with pomalidomide and dexamethasone, according to the schedule in the following Table 1:

Table 1 - SARCLISA dosing schedule in combination with pomalidomide and dexamethasone

Cycles	Dosing schedule
Cycle 1	Days 1, 8, 15 and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

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

For other medicinal products that are administered with Sarclisa, refer to the respective current Product Information.

The administration schedule must be carefully followed. 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.

Method of administration

Preparation for the intravenous administration

The preparation of the infusion solution must be done under aseptic conditions.

- The dose (mg) of required Sarclisa concentrated injection should be calculated based on patient weight (measured prior to each cycle to have the administered dose adjusted accordingly, see section 4.2). More than one SARCLISA concentrate vial may be necessary to obtain the required dose for the patient.
- Vials of Sarclisa concentrated injection should be visually inspected before dilution to ensure they don't contain any particles and are not discolored.
- The appropriate volume of Sarclisa concentrated injection should be withdrawn and diluted in an infusion bag with 250 mL of 9 mg/mL (0.9%) of sodium chloride or dextrose 5% solution to achieve the appropriate Sarclisa concentration 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.

Administration

- The infusion solution must be administered by intravenous infusion using an IV tubing infusion set (in PE, PVC with or without DEHP, polybudadiene (PBD) or polyurethane (PU)) with an 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 section 4.2).
- Prepared Sarclisa infusion solution should be used within 48 hours when stored at 2°C - 8°C, followed by 8 hours (including the infusion time) at room temperature.
- No protection from light is required for the prepared infusion bag in a standard artificial light environment.
- Do not infuse Sarclisa solution concomitantly in the same intravenous line with other agents.

Infusion rates

Following dilution, the SARCLISA infusion should be administered intravenously at the infusion rate presented in the Table 2 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions (IR). (see section 4.8)

Table 2 - Infusion rates of Sarclisa administration

	Dilution volume	Initial rate (1st hour)	Absence of IR	Rate increment	Maximum rate
First infusion	250 mL	25 mL/ hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/ hour
Second infusion	250 mL	50 mL/ hour	For 30 minutes	50 mL/ hour for 30 minutes then increase by 100 mL/ hr every 30 minutes	200 mL/ hour
Subsequent infusions	250 mL	200 mL/ hour	_____	____	200 mL/ hour

Dosage adjustment

No dose reduction of Sarclisa is recommended.

Administration adjustments should be made if patients experience the following adverse reactions:

Infusion reactions (IRs)

- In patients who experience an IR, a temporary interruption in the infusion should be considered and additional symptomatic medication can be administered. After improvement, Sarclisa infusion may be resumed at half of the initial infusion rate under close monitoring and supportive care, as needed. 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 Table 2 (see section 4.4).
- If symptoms do not resolve rapidly or improve after interruption of Sarclisa infusion, recur after initial improvement with appropriate medications, or require hospitalization or are life-threatening, treatment with Sarclisa should be permanently discontinued and additional supportive therapy should be administered, as needed.

Neutropenia

In the event of grade 4 neutropenia, Sarclisa administration should be delayed until neutrophil count recovers to at least 1.0 x 10^9/L. The use of growth factors (e.g. G-CSF) should be considered, according to local guidelines. (see section 4.4)

For other medicinal products that are administered with Sarclisa, refer to the respective current Product Information.

Special populations:

Paediatric population

The safety and efficacy of Sarclisa in children below 18 years of age have not been established.

Elderly

Based on population pharmacokinetic analysis, no dose adjustment is recommended in elderly patients.

Patients with renal impairment
Based on population pharmacokinetic analysis and on clinical safety, no dose adjustment is recommended in patients with mild to severe renal impairment (see section 5.2).

Patients with hepatic impairment
Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment. Limited data are available in patients with moderate hepatic impairment, and no data are available in patients with severe hepatic impairment (see section 5.2).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

The Product Information for all medicinal products used in combination with Sarclisa must be consulted before starting Sarclisa therapy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infusion reactions

Infusion reactions (IRs), mostly mild or moderate, have been observed in 38.2% of patients treated with Sarclisa. All IRs started during the first Sarclisa infusion and resolved on the same day in most patients. The most common symptoms of an IR included dyspnoea, cough, chills and nausea. The most common severe signs and symptoms included hypertension and dyspnoea (see section 4.8).

To decrease the risk and severity of IRs, patients should be pre-medicated prior to Sarclisa infusion with acetaminophen, H2 antagonists or proton pump inhibitors, diphenhydramine or equivalent; dexamethasone is to be used as both premedication and anti-myeloma treatment. Vital signs should be frequently monitored during the entire Sarclisa infusion. When required, interrupt Sarclisa infusion and provide appropriate medical and supportive measures (see section 4.2). In case symptoms do not improve after interruption of Sarclisa infusion, recur after initial improvement with appropriate medications, require hospitalization or are life-threatening, permanently discontinue Sarclisa and institute appropriate management.

Neutropenia

Grade 3-4 neutropenia reported as laboratory abnormalities (84.9%) and neutropenic complications (30.3%) have been observed in patients treated with Sarclisa (see section 4.8).

Monitor complete blood cell counts periodically during treatment. Antibiotics, antifungal and antiviral prophylaxis can be considered during treatment. Monitor patients with neutropenia for signs of infection. No dose reductions of Sarclisa are recommended. Sarclisa dose delays and the use of colony-stimulating factors (e.g. G-CSF) may be required to allow improvement of neutrophil count (see section 4.2).

Infection

A higher incidence of infections including grade ≥ 3 infections, mainly pneumonia, upper respiratory tract infection and bronchitis, occurred with the isatuximab regimen (see section 4.8). Patients receiving isatuximab regimen should be closely monitored for signs of infection and appropriate standard therapy instituted. Antibiotics, antifungal and antiviral prophylaxis can be considered during treatment.

Use in the elderly

Based on population pharmacokinetic analysis, no dose adjustment is recommended in elderly patients.

Paediatric use

The safety and efficacy of Sarclisa in children below 18 years of age have not been established.

Effects on laboratory tests

Interference with Serological Testing (indirect antiglobulin test)

Isatuximab binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA-MM, the indirect antiglobulin test was positive during Isa-Pd treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by isatuximab treatment. To avoid potential problems with RBC 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. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices (see section 4.5).

Interference with the response assessment

Isatuximab is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) 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. Twenty-two patients in the Isa-Pd arm who met VGPR criteria with only residual immunofixation-positivity were tested for interference. Serum samples from these patients were tested by mass spectrometry to separate isatuximab signal from the myeloma M-protein signal. In 11 out of 22 patients, there was no residual myeloma M-protein detectable at the sensitivity level of the immunofixation test (25 mg/dL); 10 of the 11 patients had IgG subtype myeloma at baseline, showing isatuximab interference with the immunofixation assay (see section 4.5).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Sarclisa has no impact on the pharmacokinetics of pomalidomide (see section 5.2).

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), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with Sarclisa (see section 4.4).

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Sarclisa may be incidentally detected by serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the monitoring of M-protein and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria (see section 4.4).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human and animal data are available to determine potential effects of Sarclisa on fertility in males and females.

Use in pregnancy – Category C

There are no available data on Sarclisa use in pregnant women. Animal reproduction toxicity studies have not been conducted with Sarclisa. No conclusions can be drawn regarding whether or not Sarclisa is safe for use during pregnancy.

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. Women of childbearing potential treated with Sarclisa should use effective contraception during treatment and for at least 5 months after cessation of Sarclisa treatment.

Sarclisa is used in combination with pomalidomide and dexamethasone. Refer to the current Product Information document for those products for further advice on use in pregnancy. In particular, pomalidomide may cause birth defects or death to an unborn baby. Patients receiving Sarclisa in combination with pomalidomide and dexamethasone should adhere to the pregnancy prevention program for pomalidomide.

Use in lactation

There are no available data on the presence of Sarclisa in human milk, milk production, or the effects on the breastfed infant. Maternal IgG is known to be excreted in human milk, but does not enter the neonatal and infant circulations in substantial amounts as the protein molecules are degraded in the gastrointestinal tract and not absorbed. No conclusions can be drawn regarding whether or not Sarclisa is safe for use during breastfeeding. The use of Sarclisa in breastfeeding women is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. On the basis of reported adverse reactions, Sarclisa is not expected to influence the ability to drive and use machines (see sections 4.2 and 4.8). Fatigue and dizziness, however, have been reported in patients taking Sarclisa and this should be taken into account when driving or using machines.

For other medicinal products that are administered with Sarclisa, refer to the respective Product Information.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial

The following CIOMS frequency rating is used: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data).

Within each frequency grouping, relevant, adverse reactions are presented in order of decreasing seriousness.

Combination therapy with Sarclisa with pomalidomide and low- dose dexamethasone in multiple myeloma

Summary of the safety profile

The safety data described in this section are based on ICARIA-MM, a randomised, open-label clinical trial in patients with previously treated multiple myeloma. In ICARIA-MM, Sarclisa 10 mg/kg was administered in combination with pomalidomide and dexamethasone (see section 5.1).

The most frequent adverse reactions (in >20% of Isa-Pd patients) were neutropenia (laboratory abnormality, 96.1% with Isa-Pd vs 93.2% with Pd), infusion reactions (38.2% with Isa-Pd vs 0% with Pd), pneumonia (30.9% with Isa-Pd vs 22.8% with Pd), upper respiratory tract infection (28.3% with Isa-Pd vs 17.4% with Pd), diarrhoea (25.7% with Isa-Pd vs 19.5% with Pd) and bronchitis (23.7% with Isa-Pd vs 8.7% with Pd). The most frequent treatment-related serious adverse reactions (in > 5% of patients) were pneumonia (9.9% with Isa-Pd vs 5.4% with Pd) and febrile neutropenia (6.6% with Isa-Pd vs 2.0% with Pd).

Permanent discontinuation of treatment because of adverse events was reported in 11 patients (7.2%) treated with Sarclisa 10 mg/kg in combination with pomalidomide and low-dose dexamethasone (Isa-Pd) and in 19 patients (12.8%) treated with pomalidomide and low-dose dexamethasone (Pd).

Tabulated list of adverse reactions

The following tables Table 3 and Table 4 present the adverse reactions observed during the treatment period in 301 patients with multiple myeloma, treated with Sarclisa 10 mg/kg in combination with pomalidomide and low-dose dexamethasone (Isa-Pd) versus pomalidomide and low-dose dexamethasone (Pd) (see section 5.1).

Table 3 - Adverse Reactions Reported in ≥ 10% of Patients and ≥5% Higher in the Isa-Pd Group Versus Pd Group - ICARIA-MM study

System Organ Class Preferred Term	Frequency	Sarclisa+ Pomalidomide + low-dose Dexamethasone (N=152) n(%)			Pomalidomide + low-dose Dexamethasone (N=149) n(%)		
		All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Infusion reaction	Very common	58 (38.2)	2 (1.3)	2 (1.3)	0	0	0
Infections and infestations							
Pneumonia [a]	Very common	47 (30.9)	33 (21.7)	5 (3.3)	34 (22.8)	24 (16.1)	4 (2.7)
Upper respiratory tract infection	Very common	43 (28.3)	5 (3.3)	0	26 (17.4)	1 (0.7)	0
Bronchitis	Very common	36 (23.7)	5 (3.3)	0	13 (8.7)	1 (0.7)	0
Blood and lymphatic system disorders							
Febrile neutropenia	Very common	18 (11.8)	16 (10.5)	2 (1.3)	3 (2.0)	2 (1.3)	1 (0.7)
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	Very common	23 (15.1)	6 (3.9)	0	15 (10.1)	2 (1.3)	0
Gastrointestinal disorders							
Diarrhea	Very common	39 (25.7)	3 (2.0)	0	29 (19.5)	1 (0.7)	0
Nausea	Very common	23 (15.1)	0	0	14 (9.4)	0	0
Vomiting	Very common	18 (11.8)	2 (1.3)	0	5 (3.4)	0	0

[a] The term pneumonia is a grouping of the following terms: 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, pneumocystis jirovecii pneumonia

Table 4 - Treatment Emergent Haematology Laboratory Abnormalities in Patients Receiving IPd Treatment Versus Pd Treatment - ICARIA-MM

Laboratory parameter	Sarclisa + Pomalidomide + low-dose Dexamethasone (N=152) n(%)[a]			Pomalidomide + low-dose Dexamethasone (N=149) n(%)[a]		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Anaemia	151 (99.3)	48 (31.6)	0	145 (98.6)	41 (27.9)	0
Neutropenia	146 (96.1)	37 (24.3)	92 (60.5)	137 (93.2)	57(38.8)	46 (31.3)
Lymphopenia	140 (92.1)	64 (42.1)	19 (12.5)	137 (93.2)	52 (35.4)	12 (8.2)
Thrombocytopenia	127 (83.6)	22 (14.5)	25 (16.4)	118 (80.3)	14 (9.5)	22 (15.0)

[a]The denominator used for the percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

Description of selected adverse reactions in multiple myeloma for isatuximab 10 mg/mL in combination with pomalidomide and low-dose dexamethasone

Infusion reactions

In ICARIA-MM, infusion reactions (IRs, 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 patients (38.2%) treated with Sarclisa. All patients who experienced IRs, experienced them during the 1st infusion of Sarclisa, with 3 patients (2.0%) also having IRs at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 IRs were reported in 3.9%, Grade 2 in 31.6%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher IRs included dyspnoea, hypertension and bronchospasm. The incidence of infusion interruptions because of infusion reactions was 28.9%. The median time to infusion interruption was 55 minutes. The median duration of Sarclisa infusion was 3.3 hours during the first infusion and 2.8 hours for the subsequent infusions.

In a separate study (TCD14079 Part B) with Sarclisa 10 mg/kg administered from a 250 mL fixed infusion volume in combination with Pd, IRs (all Grade 2) were reported in 47.1% of patients, at the first administration, the day of the infusion. The median duration of infusion was 3.94 hours for the first infusion, 1.88 hours for the second infusion, and 1.25 hours from third infusion onwards. Overall, the safety profile of Sarclisa 10 mg/kg administered as a 250 mL fixed infusion volume was similar to that of Sarclisa as administered in ICARIA-MM.

Infections

In ICARIA-MM, the incidence of Grade 3 or higher infections was 42.8%. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 21.7% of patients in Isa-Pd group compared to 16.1% in Pd group, and Grade 4 in 3.3% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in Isa-Pd group compared to 5.4% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and 4.0% in Pd group.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 OVERDOSE

Signs and symptoms

There has been no experience of overdose in clinical studies. Doses of intravenous Sarclisa up to 20 mg/kg have been administered in clinical studies.

Management

There is no known specific antidote for Sarclisa overdose. In the event of overdose of Sarclisa, monitor the patients for signs or symptoms of adverse effects and take all appropriate measures immediately.

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: CD38 directed monoclonal antibody, ATC code: not yet assigned.

Mechanism of action

Isatuximab is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of CD38 receptor and triggers several mechanisms leading to the death of CD38 expressing tumuor cells.

CD38 is a transmembrane glycoprotein with ectoenzymatic activity, expressed in haematological malignancies, and is highly and uniformly expressed on multiple myeloma cells.

Isatuximab acts through IgG Fc-dependent mechanisms including: antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Isatuximab can also trigger tumuor cell death by induction of apoptosis via an Fc-independent mechanism.

In human peripheral blood mononuclear cells (PBMCs), natural killer (NK) cells express the highest CD38 levels. *In vitro*, isatuximab can activate NK cells in the absence of CD38 positive target tumour cells through a mechanism which is dependent of the Fc portion of isatuximab. Also, isatuximab inhibits regulatory T cells (Tregs) which express higher levels of CD38 in MM patients compared to healthy individuals.

Isatuximab blocks the enzymatic activity of CD38 which catalyses the synthesis and hydrolysis of cyclic ADP-ribose(cADPR), a calcium mobilising agent, and this may contribute to immunoregulatory functions. Isatuximab inhibits the cADPR production from extracellular nicotinamide adenine dinucleotide (NAD) in multiple myeloma cells.

The combination of isatuximab and pomalidomide *in vitro* enhances cell lysis of CD38 expressing multiple myeloma cells by effector cells (ADCC), and by direct tumour cell killing compared to that of isatuximab alone. *In vivo* experiments using a human multiple myeloma xenograft model demonstrated that the combination of isatuximab and pomalidomide results in enhanced antitumour activity compared to the activity of isatuximab or pomalidomide alone.

Pharmacodynamic effects

The pharmacodynamic of isatuximab was characterized in monotherapy. A decrease in absolute counts of total NK cells (including inflammatory $CD16^{+\ low}$ $CD56^{+\ bright}$ and

cytotoxic $CD16^{+}$ ^{bright} $CD56^{+}$ ^{dim} NK cells), $CD19^{+}$ B-cells, $CD4^{+}$ T-cells and T_{REG} ($CD3^{+}$, $CD4^{+}$, $CD25^{+}$, $CD127^{-}$) was observed in peripheral blood. The decrease of the T_{REG} was higher in responder patients compared to non-responder patients.

T-cell receptor (TCR) DNA sequencing was used to quantify expansion of individual T-cell clones, each of them having a unique TCR conferring antigen specificity. In multiple myeloma patients, Sarclisa monotherapy induced clonal expansion of the T-cell receptor repertoire.

Two multiple myeloma patients who had a clinical response under Sarclisa treatment, developed T-cell responses against CD38 and tumor-associated antigens. In the same monotherapy study two patients who did not respond to Sarclisa did not develop such T-cell response.

In multiple myeloma patients treated with Sarclisa combined with pomalidomide and dexamethasone, a decrease in absolute counts of total NK cells (including inflammatory $CD16^{+}$ ^{low} $CD56^{+}$ ^{bright} and cytotoxic $CD16^{+}$ ^{bright} $CD56^{+}$ ^{dim} NK cells) and $CD19^{+}$ B-cells was observed in peripheral blood. An increase of $CD4^{+}$ T cells and T_{REG} ($CD3^{+}$, $CD4^{+}$, $CD25^{+}$, $CD127^{-}$) was observed in the all treated population and non-responder patients.

The pharmacodynamics effects of Sarclisa in multiple myeloma patients support its immunomodulatory mechanism of action. In addition to its effector functions, Sarclisa induced T-cell response indicating an adaptive immune response.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity to Sarclisa.

In ICARIA-MM, no patients tested positive for anti-drug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single agent and combination therapies including ICARIA-MM (N=564), the incidence of treatment emergent ADAs was 2.3%. No effect of ADAs was observed on pharmacokinetics, safety or efficacy of Sarclisa.

Clinical trials

ICARIA-MM (EFC14335)

The efficacy and safety of Sarclisa in combination with pomalidomide and low-dose dexamethasone were evaluated in ICARIA-MM (EFC14335), a multicenter, multinational, randomised, open-label, 2-arm, phase III study in patients with relapsed and refractory multiple myeloma. Patients had received at least two prior therapies including lenalidomide and a proteasome inhibitor.

A total of 307 patients were randomised in a 1:1 ratio to receive either Sarclisa in combination with pomalidomide and low-dose dexamethasone (Isa-Pd, 154 patients) or pomalidomide and low-dose dexamethasone (Pd, 153 patients). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. Sarclisa 10

mg/kg was administered as an I.V. infusion weekly in the first cycle and every two weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (PO/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.

Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 67 years (range 36-86), 19.9% of patients were ≥75 years, 10.4% of patients entered the study with a history of COPD or asthma, and 38.6% versus 33.3% of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) were included in Isa-Pd versus Pd groups, respectively. The International Staging System (ISS) Stage at initial diagnosis was I in 25.1%, II in 31.6% and III in 28.0% of patients. Overall, 19.5% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14) and t(14;16) were present in 12.1%, 8.5% and 1.6% of patients., respectively.

The median number of prior lines of therapy was 3 (range 2-11). All patients received a prior proteasome inhibitor, all patients received prior lenalidomide, and 56.4% of patients received prior stem cell transplantation. The majority of patients (92.5%) were refractory to lenalidomide, 75.9% to a proteasome inhibitor, and 72.6% to both an immunomodulatory and a proteasome inhibitor, and 59% of patients were refractory to lenalidomide at last line of therapy.

The median duration of treatment was 41.0 weeks for Isa-Pd group compared to 24.0 weeks for Pd group.

Progression free survival (PFS) was the primary efficacy endpoint of ICARIA-MM. The improvement in PFS represented a 40.4% reduction in the risk of disease progression or death in patients treated with Isa-Pd.

Efficacy results are presented in the Table 5 and Kaplan-Meier curves for PFS and OS are provided in Figure 1 and Figure 2:

Table 5 - Efficacy of Sarclisa in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

Endpoint	Sarclisa + pomalidomide + low-dose dexamethasone N =154	Pomalidomide + low-dose dexamethasone N = 153
Progression-Free Survival[a]		
Median (months) [95% CI][f]	11.53 [8.936-13.897]	6.47 [4.468-8.279]
Hazard ratio[d] [95% CI]	0.596 [0.436-0.814]	
p-value (stratified log-rank test)[d]	0.0010	
Overall Response Rate[b]		
Responders (sCR+CR+VGPR+PR) n(%) [95% CI][c]	93 (60.4) [0.5220-0.6817]	54 (35.3) [0.2775-0.4342]
Odds ratio vs Pd [95% exact CI]	2.795 [1.715-4.562]	

Endpoint	Sarclisa + pomalidomide + low-dose dexamethasone N =154	Pomalidomide + low-dose dexamethasone N = 153
Progression-Free Survival[a]		
Median (months)	11.53	6.47
[95% CI][f]	[8.936-13.897]	[4.468-8.279]
Hazard ratio[d] [95% CI]	0.596 [0.436-0.814]	
p-value (stratified log-rank test)[d]	0.0010	
p-value (stratified Cochran-Mantel-Haenszel)[d]	<0.0001	
Stringent Complete Response (sCR) + Complete Response (CR) n(%)	7 (4.5)	3 (2.0)
Very Good Partial Response (VGPR) n(%)	42 (27.3)	10 (6.5)
Partial Response (PR) n(%)	44 (28.6)	41 (26.8)
VGPR or better n(%)	49 (31.8)	13 (8.5)
[95% CI][c]	[0.2455-0.3980]	[0.0460-0.1409]
Odds ratio vs Pd [95% exact CI]	5.026 [2.514-10.586]	
p-value (stratified Cochran-Mantel Haenszel)[d]	<0.0001	
Duration of Response[e] *(PR or better)		
Median in months [95% CI][f]	13.27 [10.612-NR]	11.07 [8.542-NR]
Minimal Residual Disease negative rate[g] (%)	5.2	0

[a] PFS results were assessed by an Independent Response Committee based on central laboratory data for M-protein and central radiologic imaging review using the International Myeloma Working Group (IMWG) criteria.
[b] sCR, CR, VGPR and PR were evaluated by the IRC using the IMWG response criteria.
[c] Estimated using Clopper-Pearson method.
[d] Stratified on age (<75 years versus >75 years) and number of previous lines of therapy (2 or 3 versus >3) according to IRT.
[e] based on Responders in the ITT population. Kaplan-Meier estimates of duration of response.
[f] CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowle.
[g] based on a sensitivity level of 10^{-5} by NGS
* Cut-off date of 11-Oct-2018. Median follow-up time=11.60 months. HR<1 favors IPd arm.
NR: not reached

In patients with high-risk cytogenetics (central laboratory assessment), median PFS was 7.49 (95% CI: 2.628 to NC) in the IPd group and 3.745 (95% CI: 2.793 to 7.885) in the Pd group (HR=0.655; 95% CI: 0.334 to 1.283). PFS improvements in the IPd group were also observed in patients >75 years (HR=0.479; 95% CI: 0.242 to 0.946), with ISS stage III at study entry (HR=0.635; 95% CI: 0.363 to 1.110), with baseline creatinine clearance < 60 ml/min/1.73 m² (HR=0.502; 95% CI: 0.297 to 0.847), with > 3 prior lines of therapy (HR=0.590; 95% CI: 0.356 to 0.977), in patients refractory to prior therapy with lenalidomide (HR=0.593; 95% CI: 0.431 to 0.816) or proteasome inhibitor (HR=0.578; 95% CI: 0.405 to 0.824) and in those refractory to lenalidomide at the last line before to the study entry (HR= 0.601; 95%CI: 0.436 to 0.828).

The median time to first response in responders was 35 days in IPd group versus 58 days in Pd group. At the time for the analysis for PFS, median overall survival was not reached for

either treatment group. At a median follow-up time of 11.6 months, 27.9% of deaths in the IPd group and 36.6% of deaths in the Pd group had occurred. The hazard ratio for OS was 0.687 (95% CI: 0.461-1.023, p-value=0.0631).

Figure 1 - Kaplan-Meier Curves of PFS – ITT population – ICARIA-MM (assessment by the IRC)

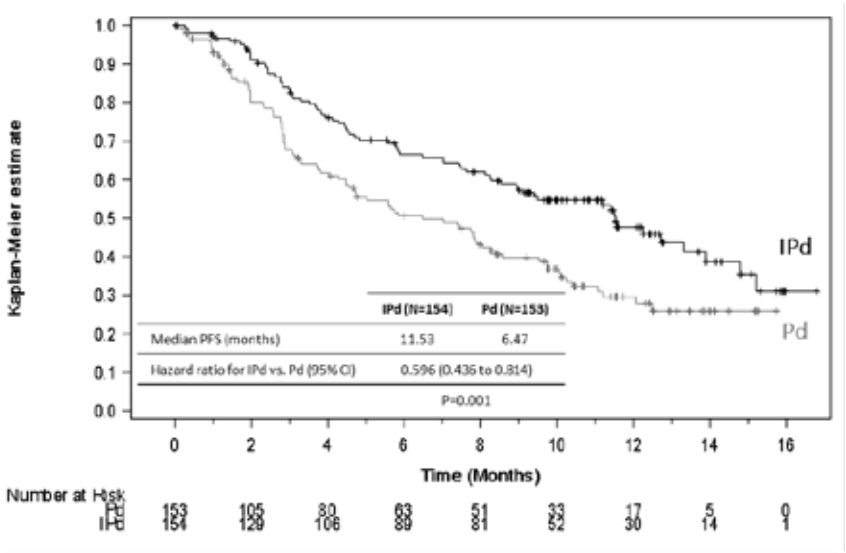
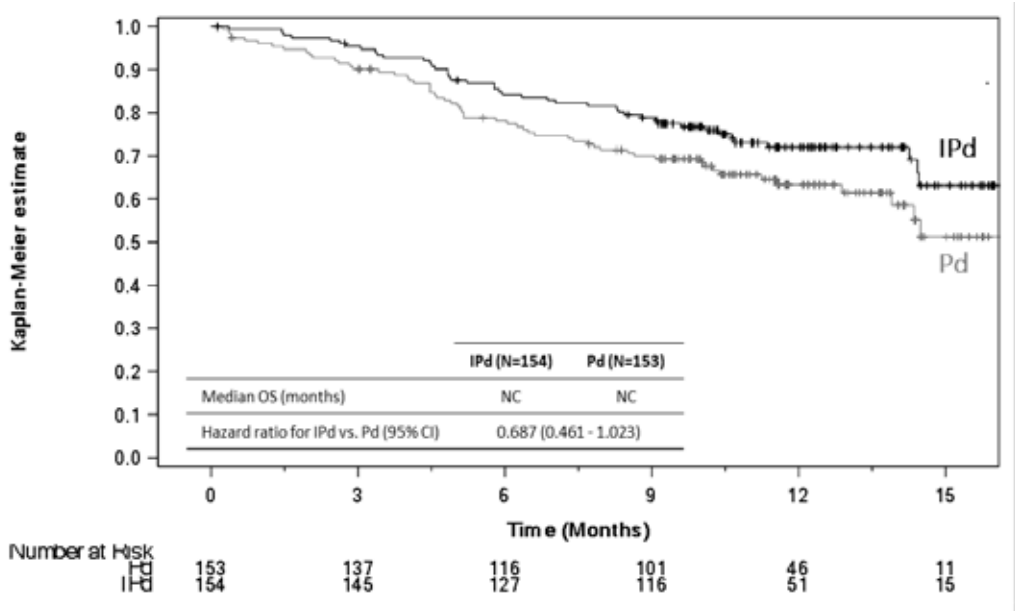


Figure 2 - Kaplan-Meier curves of OS – ITT population – ICARIA-MM



Cutoff date = 11-Oct-2018

Among patients with creatinine clearance <50 mL/min/1.73m^2 at baseline, complete renal response (≥60 mL/min/1.73m^2 at ≥1 postbaseline assessment) was observed for 71.9% of patients in the IPd group and 38.1% in the Pd group. Sustained complete renal response (>60 days) occurred in 31.3% of patients in the IPd group and in 19.0% in the Pd group (see section 4.2).

Overall, the quality of life assessed by Global Health Status Score (QLQ-C30) was maintained during treatment and similar in both treatment groups.

TCD14079

In a multicenter, 2-part, open-label, non-comparative Phase Ib study (TCD14079 Part A and B), Sarclisa 10 mg/kg was administered in combination with pomalidomide and low-dose dexamethasone (Isa-Pd) to patients with relapsed/ refractory multiple myeloma (same treatment regimen and similar patient population and characteristics as in ICARIA-MM). The median duration of treatment was 41.0 weeks. Of the 31 patients evaluable for efficacy in Part A, the ORR was 64.5% and the median PFS was 17.58 months (95% CI: 6.538 to not reached) with a median duration of follow-up of 8.6 months. Efficacy results were consistent with ICARIA-MM results. The Part B of the study investigated a fixed infusion volume (see section 4.8).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of isatuximab were assessed in 476 patients with multiple myeloma treated with isatuximab intravenous infusion as a single agent or in combination with pomalidomide/ dexamethasone, at doses ranging from 1 to 20 mg/kg, administered either once weekly; every 2 weeks; or every 2 weeks for 8 weeks followed by every 4 weeks; or every week for 4 weeks followed by every 2 weeks.

Isatuximab displays nonlinear pharmacokinetics with target-mediated drug disposition due to its binding to CD38 receptor.

Isatuximab exposure (area under the plasma concentration-time curve over the dosing interval AUC) increases in a greater than dose proportional manner from 1 to 20 mg/kg following every 2 weeks schedule, while no deviation to the dose proportionality is observed between 5 and 20 mg/kg following every week for 4 weeks followed by every 2 weeks schedule. After isatuximab 10 mg/kg administration every week for 4 weeks followed by every 2 weeks, the median time to reach steady state was 8 weeks with a 3.1-fold accumulation., The mean (CV%) predicted maximum plasma concentration C_{max} and AUC at steady state were 351 µg/mL (36.0%) and 72,600 µg.h/mL (51.7%), respectively.

Distribution

The estimated total volume of distribution of isatuximab is 8.75 L.

Metabolism

As a large protein, isatuximab is expected to be metabolized by non-saturable proteolytic catabolism processes.

Elimination

Isatuximab is eliminated by two parallel pathways, a nonlinear target-mediated pathway predominating at low concentrations, and a nonspecific linear pathway predominating at higher concentrations. In the therapeutic plasma concentrations range, the linear pathway is

predominant and decreases over time by 50% to a steady state value of 0.00955 L/h (0.229 L/day). This is associated with a terminal half-life of 28 days.

Drug Interactions

The pharmacokinetics of isatuximab and pomalidomide were not influenced by their coadministration.

Special population

Age, gender and race
The population pharmacokinetic analyses of 476 patients aged 36 to 85 years showed comparable exposure to isatuximab in patients < 75 years old versus > 75 years old (n=70). Gender and race had no clinically meaningful effect on isatuximab pharmacokinetics.

Weight
Isatuximab exposure (AUC) at steady state decreased with increasing body weight.

Hepatic Impairment
No formal studies of isatuximab in patients with hepatic impairment have been conducted. Out of the 476 patients of the population pharmacokinetic analyses, 65 patients presented with mild hepatic impairment [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate amino transferase (AST) > ULN] and 1 patient had moderate hepatic impairment (total bilirubin> 1.5 to 3 times ULN and any AST). Mild hepatic impairment had no clinically meaningful effect on the pharmacokinetics of isatuximab. The effect of moderate (total bilirubin >1.5 times to 3 times ULN and any AST) and severe hepatic impairment (total bilirubin >3 times ULN and any AST) on isatuximab pharmacokinetics is unknown.

Renal Impairment
No formal studies of isatuximab in patients with renal impairment have been conducted. The population pharmacokinetic analyses on 476 patients included 192 patients with mild renal impairment (60 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate (e-GFR) <90 mL/min/1.73 m^2), 163 patients with moderate renal impairment (30 mL/min/1.73 m^2≤ e-GFR < 60 mL/min/1.73 m^2) and 12 patients with severe renal impairment (e-GFR <30 mL/min/1.73 m^2). Analyses suggested no clinically meaningful effect of mild to severe renal impairment on isatuximab pharmacokinetics compared to normal renal function.

Pediatric
Sarclisa was not evaluated in patients under 18 years of age.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted with SARCLISA. As a large protein molecule, isatuximab is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

Carcinogenicity studies have not been conducted with Sarclisa.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sucrose
Histidine hydrochloride monohydrate
Histidine
Polysorbate 80
Water for injections

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After dilution
Microbiological, chemical and physical in-use stability of SARCLISA infusion solution has been demonstrated for 48 hours at 2°C - 8°C, followed by 8 hours (including the infusion time) at room temperature. No protection from light is required for storage in the infusion bag.

Sarclisa is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate). Do not freeze. Do not shake.
Keep in the original package in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Sarclisa 100 mg/ 5mL concentrated injection for infusion vial

- 5 ml concentrated injection containing 100 mg of isatuximab (fill volume: 5.4 mL) in a 6 mL type I colourless clear glass vial closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stoppers. The stoppered vials are crimped with an aluminium seal with a gray flip-off button. The fill volume has been established to ensure removal of 5 mL.
- Pack size of one or three single-use vials.

Sarclisa 500 mg/25 mL concentrated injection for infusion vial

- 25 ml concentrated injection containing 500 mg of isatuximab (fill volume: 26.0 mL) in a 30 mL type I colourless clear glass vial closed with ETFE (copolymer of ethylene

and tetrafluoroethylene)-coated bromobutyl stoppers. The stoppered vials are crimped with an aluminium seal with a blue flip-off button. The fill volume has been established to ensure removal of 25 mL.

- Pack size of one single-use vial.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The protein structure of isatuximab is composed of 2 kappa light chains each with molecular weight of approximately 23 kDa and 2 IgG1 heavy chains each with a molecular weight of approximately 49 kDa (deglycosylated form) linked through disulfide bridges. Each light chain consists of 214 amino acid residues and each heavy chain consists of 450 amino acid residues.

CAS number: 1461640-62-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Australia

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Toll Free Number (medical information): 1800 818 806
E-mail: medinfo.australia@sanofi.com

New Zealand

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street
Ellerslie, Auckland
Toll Free Number (medical information): 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

06 May 2020

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information