

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **SARCLISA**™

Isatuximab for injection

Concentrate for solution for infusion (20 mg/mL)

Professed

Antineoplastic, monoclonal antibody

ATC code: L01XC38

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sarclisa (isatuximab for injection) is indicated:

- in combination with pomalidomide and dexamethasone, for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in safety and efficacy were observed between older and younger patients (see WARNINGS AND PRECAUTIONS, Geriatrics and ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics, *Geriatrics*).

2 CONTRAINDICATIONS

Isatuximab for injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- Sarclisa should be administered by a healthcare professional experienced in the treatment of cancer and with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions.
- Administer only as an intravenous infusion after dilution (see Reconstitution).

Premedication

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

- Dexamethasone 40 mg oral (PO) or intravenous (IV; or 20 mg PO or IV in patients ≥ 75 years of age).
- Acetaminophen 650 mg to 1000 mg PO (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 PO (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (PO or IV) corresponds to the total dose to be administered only once before Sarclisa infusion, as part of the premedication and of the backbone treatment; do not administer another dose.

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

3.2 Recommended Dose and Dosage Adjustment

Recommended Dose

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

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.

Refer to pomalidomide and dexamethasone Product Monographs for respective current prescribing information (see SUPPORTING PRODUCT MONOGRAPHS).

Dosage Adjustment

Health Canada has not authorized an indication for pediatric use (see INDICATIONS).

No dose adjustment is recommended in geriatric patients (≥ 65 years of age) (see ACTION AND CLINICAL PHARMACOLGY, Pharmacokinetics, *Geriatrics*).

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 ACTION AND CLINICAL PHARMACOLGY, Pharmacokinetics, *Hepatic Insufficiency*).

No dose adjustment is recommended in patients with renal impairment (see ACTION AND CLINICAL PHARMACOLGY, Pharmacokinetics, *Renal Insufficiency*).

Temporary interruption or definitive discontinuation of Sarclisa treatment may be required for infusion-related reactions (IRRs) or neutropenia; no dose reduction of Sarclisa is recommended (Table 2).

Table 2 : Adjustments for Sarclisa treatment administration following IRRs or neutropenia

Adverse Reaction	NCI-CTCAE version 4.03 criteria definition	Administration adjustment
Infusion-related reactions (IRRs)	Mild (Grade 1): Infusion interruption or intervention not indicated	- Continue Sarclisa infusion per the judgment of the physician with close direct monitoring of the patient's clinical status. - Sarclisa infusion may be stopped at any time if deemed necessary.
	Moderate (Grade 2): Infusion interruption indicated but responsive promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	- Stop Sarclisa infusion. - Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) as needed. - Sarclisa may be resumed only after patient recovery, with slower infusion rate (see Table 3) and with close monitoring.
	Severe (Grade 3) or life-threatening (Grade 4) Grade 3: prolonged symptoms (e.g., 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	- Stop Sarclisa infusion. - Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. - Discontinue Sarclisa treatment.
Neutropenia	Grade 3/4	- Sarclisa administration should be delayed until neutrophil count improves to at least $1.0 \times 10^9/L$. - The use of colony-stimulating factors (e.g. G-CSF) should be considered, according to local guidelines (see WARNINGS AND PRECAUTIONS).

NSAIDs: nonsteroidal anti-inflammatory drugs

For dosage adjustment information concerning medicinal products given in combination with Sarclisa, consult the corresponding Product Monographs (see SUPPORTING PRODUCT MONOGRAPHS).

3.3 Administration

- The infusion solution must be administered by intravenous infusion using an IV tubing infusion set (in polyethylene [PE], polyvinyl chloride [PVC] with or without di (2-ethylhexyl) phthalate [DEHP], polybutadiene [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 Infusion Rates).
- 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 rates presented in Table 3 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion related reactions (IRRs) (see Dosage Adjustment and ADVERSE REACTIONS)

Table 3: Infusion Rates of Sarclisa Administration

	Dilution Volume	Initial Rate	Absence of Infusion Reaction	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/hour every 30 minutes	200 mL/hour
Subsequent Infusions	250 mL	200 mL/hour	--	--	200 mL/hour

3.4 Reconstitution

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

- The dose (mg) of required Sarclisa concentrate should be calculated based on patient weight (measured prior to each cycle to have the administered dose adjusted accordingly, see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment). More than one Sarclisa concentrate vial may be necessary to obtain the required dose for the patient.
- Vials of Sarclisa concentrate should be visually inspected before dilution to ensure they do not contain any particles and are not discolored.
- The appropriate volume of Sarclisa concentrate should be withdrawn from Sarclisa vial and diluted in an infusion bag with 250 mL of 0.9% sodium chloride or dextrose 5% solution.
- 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 mix the diluted solution by inverting the bag. Do not shake.

3.5 Missed Dose

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.

4 OVERDOSAGE

There has been no experience of overdosage in clinical studies. Doses of intravenous Sarclisa up to 20 mg/kg have been administered in clinical studies. In the event of overdose, closely monitor patients for signs and symptoms of adverse reactions and initiate appropriate symptomatic and supportive treatment (see WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS).

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4: Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (IV) Infusion	Concentrate for solution for infusion 100 mg/5 mL (6 mL single use vial); Pack size of one or three single-use vials 500 mg/25 mL (30 mL single use vial); Pack size of one single-use vial Each mL of Sarclisa concentrate contains 20 mg of isatuximab.	Histidine, Histidine hydrochloride monohydrate, Polysorbate 80, Sucrose, Water for injection

6 WARNINGS AND PRECAUTIONS

General

Sarclisa is administered in combination with other medications; therefore, the contraindications, warnings and precautions and distribution restriction applicable for use with those medications also apply to Sarclisa combination therapy. The Product Monographs of all medications used in combination with Sarclisa should be consulted before starting the therapy (see SUPPORTING PRODUCT MONOGRAPHS).

Interference with Response Assessment

Sarclisa is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE) assays used for the clinical monitoring of endogenous myeloma (M)-protein (see DRUG INTERACTIONS, Drug-Laboratory Interactions). This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa-expressing myeloma protein. In patients with persistent very good partial response (VGPR), consider other methods to evaluate the depth of response.

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). ABO/RhD typing was not affected by Sarclisa 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 DRUG INTERACTIONS, Drug-Laboratory Test Interactions).

Driving and Operating Machinery

Fatigue and dizziness have been reported in patients taking Sarclisa. Patients should exercise caution when driving or using machines.

Hematologic

Neutropenia

In the pivotal study ICARIA-MM, Grade 3 and 4 neutropenia as laboratory abnormalities were reported in 24.3% and 60.5% of patients treated with Sarclisa in combination with pomalidomide and dexamethasone (Isa-Pd). Neutropenic complications included febrile neutropenia (11.8% of patients) and neutropenic infections (25% of patients) (see ADVERSE REACTIONS). Sarclisa infusion was omitted due to neutropenia in 9.2% of patients. Pomalidomide and dexamethasone dose reduction or omission due to neutropenia occurred in 29.6% and 9.2% of patients, respectively. Use of granulocyte-colony stimulating factor (G-CSF) was required in 69.1% of the patients, either for prophylaxis or as treatment for neutropenia.

Monitor complete blood cell counts at baseline and 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, modification of pomalidomide and dexamethasone treatment and the use of G-CSF may be required to allow improvement of neutrophil count (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Immune

Infusion-Related Reactions (IRRs)

In ICARIA-MM, IRRs, mostly Grade 1 or 2, have been observed in 38.2% of patients treated with Sarclisa in combination with pomalidomide and dexamethasone (see ADVERSE REACTIONS). Sarclisa was discontinued due to a Grade 3 or 4 IRR in 4 (2.6%) patients. All IRRs started during the first Sarclisa infusion and resolved on the same day in most patients. The most common symptoms of an IRR included dyspnea, cough, nasal congestion, chills and nausea. The most common severe signs and symptoms included hypertension and dyspnea (see ADVERSE REACTIONS).

To decrease the risk and severity of IRRs, 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 on the day of Sarclisa infusion (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Premedication). Vital signs should be frequently monitored during the entire Sarclisa infusion. In the event of an IRR in which infusion interruption or intervention (Grade 2) is indicated, interrupt Sarclisa infusion and provide appropriate medical and supportive measures (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment). In case symptoms do not improve after interruption of Sarclisa infusion, recur after initial improvement with appropriate medications, require hospitalization or are life-threatening (Grade 3 or 4), permanently

discontinue Sarclisa and institute appropriate management (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Sexual Health

Fertility

No human and animal data are available to determine potential effects of Sarclisa on fertility in males and females (see NON-CLINICAL TOXICOLOGY).

6.1 Special Populations

6.1.1 Pregnant Women

There are no available data on Sarclisa use in pregnant women. Animal reproduction toxicity studies have not been conducted with Sarclisa. Sarclisa is an immunoglobulin G1 (IgG1) monoclonal antibody which is known to cross the placenta. Based on its mechanism of action and findings in CD38-knockout mice, exposure to isatuximab may cause fetal harm, e.g., immune cell depletion, neurological deficits, decreased bone density and metabolic disorders. 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 in combination with pomalidomide is contraindicated in pregnant women and women at risk of becoming pregnant, as pomalidomide is contraindicated in these populations. Refer to pomalidomide and dexamethasone Product Monographs for requirements regarding contraception and for additional details (see SUPPORTING PRODUCT MONOGRAPHS).

6.1.2 Breast-feeding

There are no available data on the presence of Sarclisa in human milk, milk production, or the effects on the breastfed infant. Human IgG antibody is known to be present in human milk. However, the effect of exposure to isatuximab via gastrointestinal tract is unclear in breastfed infants. As there is a potential for serious adverse reactions in breastfed infants, the use of Sarclisa in breastfeeding women is not recommended.

Sarclisa in combination with pomalidomide is contraindicated in breast-feeding women, as pomalidomide is contraindicated in this population. Refer to pomalidomide and dexamethasone Product Monographs for additional details (see SUPPORTING PRODUCT MONOGRAPHS).

6.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics

In ICARIA-MM Isa-Pd group, 43.5% of patients were 65 to 74 years of age, and 21.1% were 75 to 84 years of age. No overall differences in safety and efficacy were observed between

younger (< 65 years of age) and older patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, *Geriatrics*).

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

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

The safety data described in this section are based on ICARIA-MM, a randomized, open-label clinical trial in patients with multiple myeloma. In ICARIA-MM, patients received Sarclisa 10 mg/kg in combination with pomalidomide and dexamethasone (Isa-Pd) or pomalidomide and dexamethasone (Pd) (see CLINICAL TRIALS).

The most frequent treatment-emergent adverse events (TEAEs, in >20% of Isa-Pd patients) were neutropenia, infusion reactions, pneumonia, upper respiratory tract infection, diarrhea and bronchitis.

The overall incidence of serious TEAEs was 61.8% in the Isa-Pd group and 53.7% in the Pd group. Serious TEAEs ($\geq 2\%$) with at least a 2% higher incidence in the Isa-Pd group versus the Pd group included infections (39.5% vs. 30.9%), febrile neutropenia (6.6% vs. 2.0%), neutropenia (3.3% vs. 1.3%) and infusion-related reactions (3.9% vs. 0%). Fatal adverse events (AEs) were reported in 11.2% of patients in the Isa-Pd group and 11.4% in the Pd group. Fatal AEs reported in > 1% of patients in the Isa-Pd group were pneumonia and other infections (3.3%) (see Clinical Trial Adverse Reactions).

Permanent discontinuation of treatment because of TEAEs 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). The most common TEAEs leading to treatment discontinuation in the Isa-Pd group were infections (2.6%).

Sarclisa dose reduction was not permitted in ICARIA-MM. In the Isa-Pd group, Sarclisa dose delay because of TEAEs was reported in 58.6% of patients, most frequently ($\geq 3\%$ of patients) due to neutropenia (27.0%), pneumonia (6.6%), bronchitis (4.6%), upper respiratory infection (3.9%) and diarrhea (3.9%).

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

Adverse reactions presented in Table 5 were observed during the treatment period in 301 patients in ICARIA-MM (see CLINICAL TRIALS). At the time of analysis, the median duration of exposure was 41 weeks (range 1.3 to 76.7) in the Isa-Pd arm and 24 weeks (range 1.0 to 73.7) in the Pd arm.

Table 5: Summary of treatment-emergent adverse events with an all grades incidence $\geq 5\%$ in the Isa-Pd group and with an all grades incidence difference $\geq 2\%$ between Isa-Pd group and Pd group in EFC14335 study - Safety Population

Primary System Organ Class [#] Preferred Term [#]	Pd (N=149)			Isa-Pd 10 mg/kg (N=152)		
	All Grades* (n%)	Grade 3 (n%)	Grade 4 (n%)	All grades* (n%)	Grade 3 (n%)	Grade 4 (n%)
Blood and lymphatic system disorders						
Neutropenia ^a	50 (33.6)	25 (16.8)	23 (15.4)	71 (46.7)	24 (15.8)	45 (29.6)
Febrile neutropenia	3 (2.0)	2 (1.3)	1 (0.7)	18 (11.8)	16 (10.5)	2 (1.3)
Gastrointestinal disorders						
Diarrhea	29 (19.5)	1 (0.7)	0	39 (25.7)	3 (2.0)	0
Nausea	14 (9.4)	0	0	23 (15.1)	0	0
Vomiting	5 (3.4)	0	0	18 (11.8)	2 (1.3)	0
Stomatitis	4 (2.7)	0	0	10 (6.6)	1 (0.7)	0
General disorders						
Edema peripheral	16 (10.7)	0	0	20 (13.2)	1 (0.7)	0
Immune system disorders						
Infusion related reaction ^b	0	0	0	58 (38.2)	2 (1.3)	2 (1.3)
Infections and infestations						
Upper respiratory tract infection	26 (17.4)	1 (0.7)	0	43 (28.3)	5 (3.3)	0
Pneumonia ^c	34 (22.8)	24 (16.1)	4 (2.7)	47 (30.9)	33 (21.7)	5 (3.3)
Bronchitis	13 (8.7)	1 (0.7)	0	36 (23.7)	5 (3.3)	0
Herpes viral infection ^d	4 (2.7)	0	0	15 (9.9)	1 (0.7)	0
Nasopharyngitis	7 (4.7)	0	0	14 (9.2)	0	0
Investigations						
Weight decreased	2 (1.3)	0	0	10 (6.6)	0	0
Metabolism and nutrition disorders						
Decreased appetite	7 (4.7)	1 (0.7)	0	15 (9.9)	2 (1.3)	0
Musculoskeletal and connective tissue disorders						

	Pd (N=149)			Isa-Pd 10 mg/kg (N=152)		
Primary System Organ Class [#] Preferred Term [#]	All Grades* (n%)	Grade 3 (n%)	Grade 4 (n%)	All grades* (n%)	Grade 3 (n%)	Grade 4 (n%)
Musculoskeletal chest pain	7 (4.7)	0	0	13 (8.6)	0	0
Bone pain	8 (5.4)	2 (1.3)	0	12 (7.9)	1 (0.7)	0
Muscular weakness	7 (4.7)	0	0	11 (7.2)	1 (0.7)	0
Myalgia	5 (3.4)	0	0	10 (6.6)	0	0
Nervous system disorders						
Headache	8 (5.4)	0	0	15 (9.9)	0	0
Tremor	6 (4.0)	0	0	12 (7.9)	3 (2.0)	0
Dizziness	4 (2.7)	0	0	8 (5.3)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	15 (10.1)	2 (1.3)	0	23 (15.1)	6 (3.9)	0

Pd: pomalidomide and dexamethasone; Isa-Pd: isatuximab in combination with pomalidomide and dexamethasone

^a Grade 5 neutropenia was reported in 1 patient (0.7%) in the Isa-Pd arm; considered as non-related to study treatment

^b Infusion related reaction was a TEAE considered to be related to infusion by site investigators and with onset typically within 24 hours from the start of infusion

^c Pneumonia includes TEAEs in the narrow Standard MedDRA Query (SMQ) Infective pneumonia. Grade 5 pneumonia was reported in 1 patient (0.7%) in the Pd arm and in 2 patients (1.3%) in the Isa-Pd arm.

^d Herpes viral infection includes the following list of terms: Herpes simplex, Herpes zoster, Herpes zoster disseminated, Oral herpes and Varicella

Note: Percentages are calculated using the number of treated patients as denominator.

[#]MedDRA 21.0

*CTCAE 4.03

Table 6: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving Isa-Pd 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
Anemia	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.

* CTCAE version: 4.03

Cardiac Arrhythmias

In ICARIA-MM, a higher incidence of all Grades cardiac arrhythmias TEAEs occurred in the Isa-Pd group (11.2%) compared with Pd group (2.0%). Grade ≥ 3 arrhythmias were reported in 3.3% patients in the Isa-Pd group compared with 0.7% in the Pd group. Most patients had pre-

existing cardiovascular disorders. The most common TEAE in this category in the Isa-Pd group was atrial fibrillation (4.6%; Grade ≥ 3 2.0%).

Infusion related reactions (IRRs)

In ICARIA-MM, IRRs, 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 IRRs, had the events during the 1st infusion of Sarclisa, with 3 patients (2.0%) also having IRRs at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 IRRs were reported in 3.9%, Grade 2 in 31.6%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. The incidence of infusion interruptions because of infusion-related 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, IRRs (all Grade 2) were reported in 47.1% of patients, at the first administration. The median duration of infusion was 3.9 hours for the first infusion, 1.9 hours for the second infusion and 1.3 hours from third infusion onwards.

In all patients treated with Sarclisa in the clinical studies, 46.4% patients had at least one IRR symptoms and 4.9% experienced Grade 3 or 4 symptoms. Sarclisa was discontinued due to a Grade 3 or 4 IRR in 4 (2.6%) patients. The most common symptoms of an IRR were dyspnea, cough, nasal congestion, chills and nausea. Other reported symptoms included hypertension, hypoxia, pulmonary edema, hypotension, tachycardia, syncope, bronchospasm, cytokine release syndrome, anaphylactic reaction, face edema, and hyperglycemia.

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.

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.

Second Primary Malignancies (SPMs)

In ICARIA-MM, 6 (3.9%) patients were diagnosed with SPMs in the Isa-PD group compared with 1 (0.7%) in the Pd group. The SPMs in the Isa-PD group were 4 cases of squamous cell carcinoma of skin, 1 post-radiation breast angiosarcoma and 1 myelodysplastic syndrome (MDS). None of the patients discontinued treatment because of the SPMs, with the exception of

the patient who developed MDS. In all patients exposed to isatuximab in clinical studies, SPMs were diagnosed in 3.0% patients.

7.3 Less Common Clinical Trial Adverse Reactions

Other TEAEs of clinical relevance in the Isa-Pd arm in ICARIA-MM include:

Blood and lymphatic system disorders: anemia.

Eye disorders: cataract; vision blurred.

Gastrointestinal disorders: abdominal distension; abdominal pain upper; gastroesophageal reflux disease.

General disorders and administration site conditions: pyrexia.

Immune system disorders: cytokine release syndrome.

Infections and infestations: influenza; Pneumocystis jirovecii pneumonia; sepsis.

Investigations: gamma-glutamyltransferase increased.

Metabolism and nutrition disorders: diabetes mellitus; hyperglycemia.

Musculoskeletal and connective tissue disorders: joint swelling; arthralgia.

Neoplasms benign, malignant and unspecified (incl cysts and polyps): squamous cell carcinoma of skin.

Nervous system disorders: dizziness; lethargy.

Psychiatric disorders: anxiety; confusional state; agitation; restlessness.

Renal and urinary disorders: urinary incontinence.

Respiratory, thoracic and mediastinal disorders: hiccups, pulmonary embolism.

Vascular disorders: hypertension; hot flush.

8 DRUG INTERACTIONS

8.1 Drug-Drug Interactions

The pharmacokinetics of isatuximab and pomalidomide were not influenced by their co-administration.

8.2 Drug-Food Interactions

Interactions with food have not been established.

8.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.4 Drug-Laboratory Test 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), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with Sarclisa (see WARNINGS AND PRECAUTIONS). 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 Sarclisa treatment.

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 WARNINGS AND PRECAUTIONS). Twenty-two patients in the Isa-Pd arm who met very good partial response (VGPR) criteria with only residual immunofixation-positivity were tested for interference. Serum samples from these patients were tested by mass spectrometry to separate Sarclisa signal from the myeloma M protein signal. In 11 out of the 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, indicating Sarclisa interference with the immunofixation assay. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Isatuximab is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of CD38 and triggers several mechanisms leading to the death of CD38 expressing tumour cells. CD38 is a transmembrane glycoprotein with ectoenzymatic activity, expressed in hematological malignancies, including multiple myeloma cells, as well as other cell types and tissues at various levels.

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 tumour cell death by induction of apoptosis via an Fc-independent mechanism.

Isatuximab inhibits the enzymatic activity of CD38 which catalyzes the synthesis and hydrolysis of cyclic ADP-ribose (cADPR), which 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 tumor 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 antitumor activity compared to the activity of isatuximab or pomalidomide alone.

9.2 Pharmacodynamics

NK Cell, CD19⁺ B-cell, CD4⁺ T-cell and TREG Cell Count

The pharmacodynamic activity 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.

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 tumor cells through a mechanism which is dependent of the Fc portion of isatuximab.

Also, isatuximab inhibits Tregs which express higher levels of CD38 in MM patients compared to healthy individuals. The decrease of the T_{REG} was higher in the 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.

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.

Cardiac Electrophysiology

The relationship between isatuximab plasma concentration and QT interval and other electrocardiogram parameters was analyzed by PK/PD modeling. Patients included in the modeling received single agent Sarclisa up to 20 mg/kg QW which resulted in an isatuximab plasma concentration consistent with the predicted steady state C_{max} of isatuximab administered at the recommended dose.

Isatuximab had no apparent effect on Frederica-corrected QT interval (QTcF) change from baseline and on PR or QRS interval.

A concentration-related effect on heart rate (HR) was demonstrated by the PK/PD modeling. The predicted geometric mean HR change from baseline for Sarclisa administered at the recommended dose is 13 beats per minutes (bpm) (95% CI: 9.3, 16.6).

9.3 Pharmacokinetics

The pharmacokinetics of isatuximab were characterized primarily by population pharmacokinetics in 476 patients with multiple myeloma treated with Sarclisa 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) increased 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 was observed between 5 and 20 mg/kg following every week for 4 weeks followed by every 2 weeks schedule.

After Sarclisa administration at the recommended dose (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 mean (CV%) predicted total volume of distribution of isatuximab is 8.13 L (26.2%).

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. The mean (CV%) clearance of isatuximab decreases over time by 50% to a

steady state value of 0.00840 L/h [0.202 L/day] (58.8%). This is associated with a mean (CV%) terminal half-life of 37 days (50%). .

Special Populations and Conditions

Pediatrics: Isatuximab was not studied in patients under 18 years of age.

Geriatrics: The population pharmacokinetic analyses of 476 patients aged 36 to 85 years showed no clinically meaningful difference in exposure to isatuximab in patients < 75 years old versus > 75 years old (n=70).

Sex: Based on population pharmacokinetic analyses, gender had no clinically meaningful effect on the pharmacokinetics of isatuximab.

Ethnic origin: Based on population pharmacokinetic analyses, race (Caucasian, Black, Asian and other races) had no clinical meaningful effect on isatuximab pharmacokinetics.

Hepatic Insufficiency: 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 Insufficiency: 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 ($60 \text{ mL/min/1.73 m}^2 \leq \text{estimated glomerular filtration rate [e-GFR]} < 90 \text{ mL/min/1.73 m}^2$), 163 patients with moderate renal impairment ($30 \text{ mL/min/1.73 m}^2 \leq \text{e-GFR} < 60 \text{ mL/min/1.73 m}^2$) and 12 patients with severe renal impairment ($\text{e-GFR} < 30 \text{ mL/min/1.73 m}^2$). Analyses suggested no clinically meaningful effect of mild to severe renal impairment on isatuximab pharmacokinetics compared to normal renal function.

10 STORAGE, STABILITY AND DISPOSAL

Vials of Sarclisa concentrate for solution for infusion should be stored between 2°C and 8°C (36°F to 46°F) and protected from light. Do not freeze. Do not shake.

After Dilution

Sarclisa infusion solution should be prepared in sodium chloride 0.9% or dextrose 5%. 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.

Disposal

Unused portions of solution must be discarded. All materials that have been utilized for dilution and administration should be disposed of according to standard procedures.

11 SPECIAL HANDLING INSTRUCTIONS

Sarclisa must not be mixed with other medicinal products except those mentioned in the DOSAGE AND ADMINISTRATION section.

The preparation of the infusion solution must be done under aseptic conditions (refer to DOSAGE AND ADMINISTRATION).

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Isatuximab
Chemical name:	Immunoglobulin G1, anti – (human CD38 antigen) (human-Mus musculus monoclonal hu38SB19 heavy chain), disulfide with human-Mus musculus monoclonal hu38SB19 light chain, dimer
Molecular formula:	Isatuximab is composed of light and heavy chains. Each light chain consists of 214 amino acid residues and each heavy chain consists of 450 amino acid residues. The heavy chain N-terminal glutamine residue is fully converted to pyroglutamate. The majority of the heavy chain C-terminal K450 is clipped (between 9 and 11 % of C-terminal K450 using reduced peptide mapping). Isatuximab contains 32 cysteines leading to 16 disulfide bonds and two glycosylation sites located on Asparagine N300 of heavy chain.
Molecular mass:	147 825 Da (G ₀ F-G ₀ F glycosylated form)
Structural formula:	Isatuximab is an IgG₁ derived-monoclonal antibody binding selectively the human CD38 membrane protein. The protein structure 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.

Formulated Drug Substance

Physiochemical properties:	The concentrate for solution for infusion is a colorless to slightly yellow solution, essentially free of visible particulates
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13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 7: Summary of patient demographics for clinical trials in Multiple Myeloma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ICARIA-MM (EFC14335)	Phase 3 Multicenter, multinational, randomized, open-label, 2-arm clinical study in patients with relapsed and refractory multiple myeloma (MM)	Sarclisa (10mg/kg; IV) ^a + pomalidomide (4mg; PO) ^b + low-dose dexamethasone (40mg PO/IV; 20mg for pts ≥ 75) ^c – 154 patients Pomalidomide (4mg; PO) ^b + low-dose dexamethasone (40mg PO/IV; 20mg for pts ≥ 75) ^c – 153 patients 28-day cycle	307	67 years of age (range 36-86)	Male: 148 (48.2%) Female: 159 (51.8%)

^a administered as an IV weekly in the first cycle and every two weeks thereafter

^b 4mg taken orally once daily from day 1 to day 21 of each 28-day cycle

^c Given on days 1, 8, 15 and 22 for each 28-day cycle

IV = Intravenous; PO = Taken orally; pts = patients

13.2 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, randomized, 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. All patients had refractory disease to the last prior therapy.

Key eligibility criteria included patients aged ≥18 years with a known diagnosis of multiple myeloma with evidence of measurable disease who had received prior treatment with at least 2 prior lines of therapy for multiple myeloma including lenalidomide and a proteasome inhibitor (PI) alone or in combination, and demonstrated disease progression on or within 60 days of completion of the last therapy. Eligible patients should have Eastern Cooperative Oncology Group (ECOG) status of 0-2, platelets ≥75,000 cells/mm³, absolute neutrophil count ≥1 × 10⁹/L, creatinine clearance ≥30 mL/min (MDRD formula), and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN). Patients who had primary refractory disease or who received prior anti-CD38 therapy were not eligible.

A total of 307 patients were randomized 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). Randomization was stratified by age (<75 years versus ≥75 years) and number of previous lines of therapy (2 or 3 versus more than 3).

Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. Sarclisa 10 mg/kg was administered as an IV 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 chronic obstructive pulmonary disease (COPD) or asthma. The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) was 38.7% in Isa-Pd group versus 33.8% in Pd group. 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, 56.4% of patients received prior stem cell transplantation, and 93.5% of patients received prior alkylating agents. The majority of patients (92.5%) were refractory to lenalidomide, 75.9% to a proteasome inhibitor, and 72.6% to both an immunomodulator and a proteasome inhibitor, and 59% of patients were refractory to lenalidomide at last prior line of therapy.

The median duration of treatment was 10.3 months for Isa-Pd group compared to 6 months for Pd group.

Progression free survival (PFS) was the primary efficacy endpoint of ICARIA-MM. PFS results were assessed by an Independent Response Committee (IRC) based on central laboratory data for M-protein and central radiologic imaging review using the 2016 International Myeloma Working Group (IMWG) criteria. Key secondary efficacy endpoints included overall response rate (ORR) as per IMWG criteria and overall survival (OS).

PFS was significantly prolonged in the Isa-Pd group compared to the Pd group. The median PFS was 11.6 months (95% confidence interval [CI]: 8.9-13.9) in the Isa-Pd group versus 6.5 months (95% CI: 4.5-8.3) in the Pd group (hazard ratio [HR] = 0.596; 95% CI: 0.436-0.814, p=0.0010), representing a 40.4% reduction in the risk of disease progression or death in patients treated with Isa-Pd (Table 8, Figure 1).

Key efficacy results are presented in the following table.

Table 8: 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		
Median (months) [95%CI]	11.5 [8.9-13.9]	6.5 [4.5-8.3]
Hazard Ratio ^a [95%CI]	0.596 [0.44-0.81]	
p-value ^a (stratified-log-rank test)	0.0010	
Overall Response Rate^b		
Responders (sCR+CR+VGPR+PR) n(%) [95% CI] ^c	93 (60.4) [0.522-0.682]	54 (35.3) [0.278-0.434]
p-value (stratified Cochran-Mantel-Haenszel) ^a	< 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)

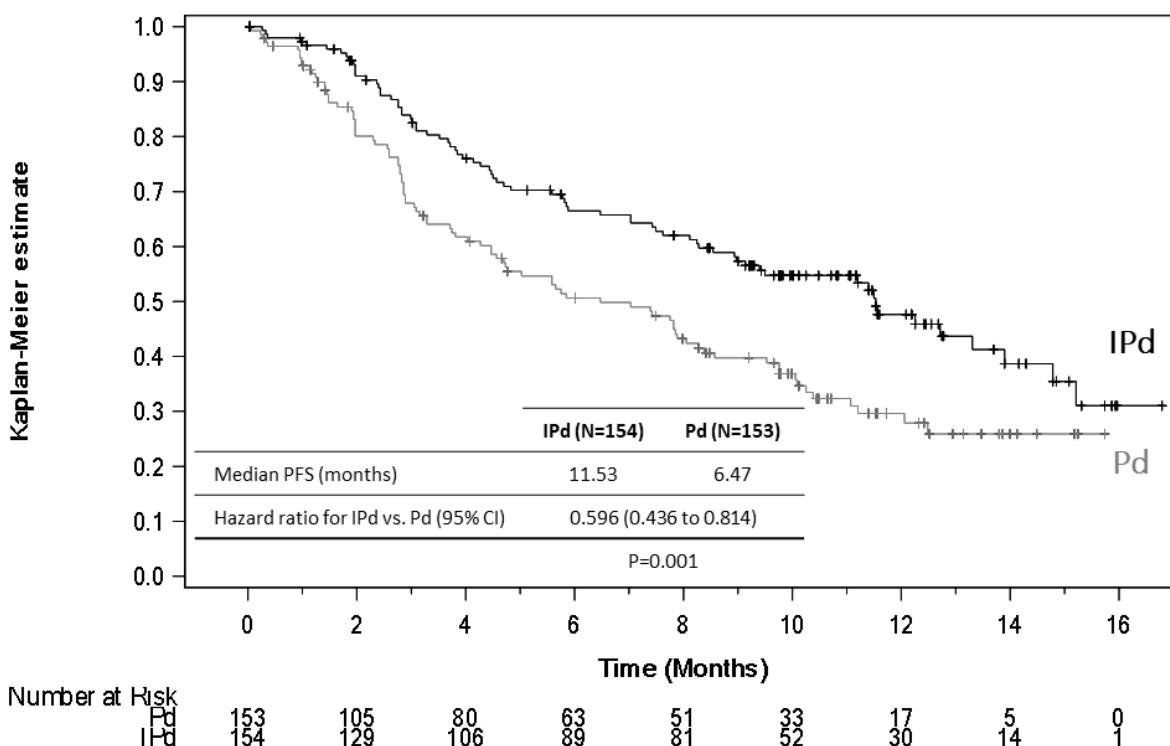
- a. Stratified on age (<75y vs ≥75 y) and number of previous lines of therapy (2 or 3 vs >3) according to IRT. The p-value for PFS was derived based on stratified log-rank test. A pre-defined hierarchical procedure allows for testing of an endpoint only when the previous one is statistically significant, in the following order: PFS, ORR and OS.
- b. sCR, CR, VGPR and PR were evaluated by the IRC using the IMWG response criteria (2016)
- c. Estimated using Clopper-Pearson method.
- CI= Confidence Interval. CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowle.

The median duration of response was 13.3 months (95% CI: 10.6-NR) in the Isa-Pd group versus 11.1 months (95% CI: 8.5-NR) in the Pd group.

Subgroup analyses based on PFS hazard ratio were generally consistent with that of the primary PFS analysis across the pre-defined subgroups, including patients with high-risk cytogenetics, > 75 years, with ISS stage III at study entry, with baseline creatinine clearance < 60 ml/min/1.73 m², with > 3 prior lines of therapy, refractory to lenalidomide or proteasome inhibitor, and refractory to lenalidomide at the last line before the study entry.

The median time to first response was 35 days in Isa-Pd group versus 58 days in Pd group. The median duration of response was 13.3 months (95% CI: 10.6-not reached [NR]) in the Isa-Pd group versus 11.0 months (95% CI: 8.5-NR) in the Pd group.

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



OS results were from a preplanned interim analysis when the primary analyses for PFS and ORR were conducted. The OS was not mature at the time of analysis. At a median follow-up time of 11.6 months, 43 (27.9%) patients on Isa-Pd and 56 (36.6%) patients on Pd had died. The hazard ratio for OS was 0.687 (95% CI: 0.461-1.023); the OS results did not reach statistical significance. Median overall survival (OS) was not reached for either treatment group.

14 NON-CLINICAL TOXICOLOGY

14.1 Genotoxicity

Genotoxicity studies have not been conducted with Sarclisa.

14.2 Carcinogenicity

Carcinogenicity studies have not been conducted with Sarclisa.

14.3 Reproductive and Developmental Toxicity

Reproductive, developmental toxicity and embryofetal toxicity studies have not been conducted with Sarclisa.

15 SUPPORTING PRODUCT MONOGRAPHS

1. Pomalyst® (pomalidomide)¹ Product Monograph. Date of revision: Aug 21, 2019
2. Dexamethasone Product Monograph.

¹ Pomalyst® is a registered trademark of Celgene Corporation

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Pr **SARCLISA** TM
Isatuximab for injection

concentrate for solution for infusion

Read this carefully before you start taking **Sarclisa (sar-KLEE-sah)** and each time you get an infusion. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Sarclisa**.

What is Sarclisa used for?

Sarclisa is used in adults 18 years or older to treat a type of cancer called multiple myeloma. This is a cancer of your plasma cells which are found in your bone marrow.

How does Sarclisa work?

Isatuximab (ee-sah-TUKS-i-mab) is the active substance of Sarclisa. It belongs to a group of medicines called “monoclonal antibodies”.

Sarclisa is used together with two other medicines called pomalidomide and dexamethasone. This treatment is for patients who have received at least 2 treatments for multiple myeloma before.

What are the ingredients in Sarclisa?

Medicinal ingredients: Isatuximab

Non-medicinal ingredients: Histidine, Histidine hydrochloride monohydrate, Polysorbate 80, Sucrose, Water for injection

Sarclisa comes in the following dosage forms:

Sarclisa is provided as a concentrate that must be diluted and is then administered by intravenous infusion. It comes in vials. Each vial of 5 mL concentrate contains 100 mg of isatuximab (concentration of 20 mg/mL). Each vial of 25 mL concentrate contains 500 mg of isatuximab (concentration of 20 mg/mL).

Do not use Sarclisa if:

- You are allergic to isatuximab or any other ingredients in Sarclisa.

If you are not sure, talk to your doctor or nurse before you receive Sarclisa.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sarclisa. Talk about any health conditions or problems you may have, including if you:

- Are pregnant, think you might be pregnant, or are planning to have a baby. If you become pregnant while being treated with Sarclisa, tell your doctor or nurse immediately. You and your doctor will decide if the benefit of receiving Sarclisa is greater than the risk to your baby. Women who are being treated with Sarclisa must use effective contraception during treatment and for at least 5 months after treatment.

- Are producing breast milk. You and your doctor will decide if the benefit of breast feeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known if it will affect the baby.

If you need a blood transfusion, you will have a blood test first to match your blood type. Sarclisa can affect the evaluation of the results of this blood test. Tell the person doing the test that you are taking Sarclisa.

Other warnings you should know about:

Infusion-Related Reactions

Infusion-related reactions can happen during Sarclisa infusion or after the infusion. Tell your doctor or nurse immediately if you experience symptoms of an infusion-related reaction. These symptoms may include

- Feeling short of breath
- Cough
- Stuffy or runny nose
- Chills
- Nausea

Severe symptoms of infusion reaction are less common, including:

- High blood pressure (hypertension)
- Low oxygen level in the blood (hypoxia)
- Low blood pressure (hypotension)
- Fast heartbeat (tachycardia)
- High level of blood sugar (hyperglycemia)
- Swollen face, lips, mouth, tongue or throat

If you have an infusion-related reaction, you may need other medicines to treat your symptoms, or the infusion may need to be slowed down or stopped. When these reactions go away or get better, the infusion can be started again.

Blood Transfusion

If you need a blood transfusion, you will have a blood test first to match your blood type. Sarclisa can affect the results of this blood test. Tell the person doing the test that you are using Sarclisa. Your doctor should do blood tests to match your blood type before you start treatment with Sarclisa.

Decreased number of White Blood Cells

Sarclisa can decrease the number of your white blood cells, which are important in fighting infections. Your doctor will monitor for your white blood cells during Sarclisa treatment. You may receive other medications to treat low white blood cells.

Infections

Sarclisa when combined with other drugs including pomalidomide and dexamethasone may increase the risk of infections. These infections can be severe or life-threatening. Tell your doctor right away if you have a fever or chill, feel very tired, have a cough or have flu-like symptoms.

Children and Adolescents

Sarclisa is not recommended for use in children and adolescents under the age of 18.

Driving and Using Machines

SARCLISA is not expected to affect your ability to drive or use machines. However, if you experience side effects of this medicine, do not drive or use machines before discussing with your doctor, pharmacist or nurse.

Abnormal Heart Rate

Sarclisa can make your heart beat faster. Tell your doctor or nurse if you have any heart problems. During Sarclisa treatment, if you feel heart racing, irregular heartbeat, dizziness, shortness of breath or chest pain, contact your doctor or nurse.

New Cancers

New cancers have happened in patients during treatment with Sarclisa. It is not clear if Sarclisa has caused the new cancers. Your doctor will monitor you for new cancers.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Sarclisa:

Your doctor or nurse will give you Sarclisa in your vein (intravenously) as a drip infusion.

Usual dose:

Your doctor will determine your dose of Sarclisa. This will depend on your body weight. The recommended dose is 10 mg of Sarclisa per kilogram of your body weight.

Sarclisa is used in treatment cycles of 28 days (4 weeks) together with pomalidomide and dexamethasone:

- In Cycle 1: SARCLISA is administered weekly on days 1, 8, 15 and 22
- In Cycle 2 and beyond: SARCLISA is administered every 2 weeks on day 1 and 15

Your doctor will continue to treat you with Sarclisa as long as you benefit from it and tolerate the potential side effects

Medicines given before an infusion of Sarclisa

You must receive the following medicines before infusion of Sarclisa to help reduce possible infusion-related reactions:

- Medicine to reduce allergic reactions (anti-histamine)
- Medicine to reduce inflammation (corticosteroid)
- Medicine to reduce pain and fever

Overdose:

Sarclisa will be given to you by your doctor or nurse. In the unlikely event that you are given too much (an overdose), your doctor will monitor you for side effects.

If you think you have taken too much Sarclisa, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is very important that you go to all your appointments to make sure your treatment works. If you miss any appointments, call your doctor or nurse as soon as possible to reschedule your appointment. Your doctor or nurse will decide how your treatment should be continued.

What are possible side effects from using Sarclisa?

These are not all the possible side effects you may feel when taking Sarclisa. If you experience any side effects not listed here, contact your healthcare professional.

- Headache
- Dizziness
- Feeling tired
- Decreased appetite
- Hiccups
- Runny or stuffy nose, sneezing, coughing, sore or scratchy throat (infection of the upper airways, such as nose, sinuses or throat)
- Nausea, vomiting
- Diarrhea
- Abdominal pain or discomfort
- Heartburn
- Swelling of the hands or legs
- Muscle, bone or joint pain
- Decreased body weight
- Feeling anxious
- Blurred vision
- High blood sugar
- Loss of bladder control (urinary incontinence)
- High blood pressure (hypertension)
- Hot flushes

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON (1 in 10 people) Infusion-related reactions Symptoms can include one or more of the following: feeling short of breath, cough, stuffy or runny nose, chills, nausea, high blood pressure (hypertension), fast heartbeat, low blood pressure, swollen face, lips, mouth, tongue or throat.			✓
Low number of blood cells such as: • Platelets (thrombocytopenia) (symptoms like unusual bruising or bleeding) • White blood cells (neutropenia or		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
lymphopenia) • Red blood cells (anemia) (symptoms like fatigue, loss of energy, weakness, shortness of breath)			
Lung infection such as pneumonia, bronchitis, lower respiratory tract infections Symptoms can include congestion, cough (may produce phlegm), body ache, tiredness, wheezing, shortness of breath, chest pain when breathing or cough, fever, sweating and chill, and confusion or change of mental awareness (mostly in older patients).		✓	
Shortness of breath		✓	
COMMON (less than 1 in 10, but more than 1 in 100) Herpes viral infection The infection can present as cold sore, shingles, or chickenpox. The symptoms can include sore on the lip or in the mouth, painful blisters on the skin, fever, feeling tired, body ache, rash, and red spots and blisters over the entire body.	✓		
Irregular or rapid heartbeat Symptoms can include heart racing, irregular heartbeat, dizziness, shortness of breath and chest pain.		✓	
Squamous cell carcinoma of the skin It may appear as a firm, red nodule, or a flat sore with a rough scaly patch on the skin, lips or inside the mouth.		✓	
Pulmonary embolism. Symptoms can include sudden feeling short of breath, sharp chest pain, cough, heart racing, sweating, feeling anxious and fainting.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Sarclisa should not be used after the expiry date which is stated on the label and carton.

Sarclisa should be stored in a refrigerator (2°C to 8°C), in its original package to protect from light.

Do not freeze.

Keep out of reach and sight of children.

If you want more information about Sarclisa:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the Sanofi-aventis Canada website www.sanofi.ca, or by calling 1-800-265-7927.

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Last Revised: