Drug Monograph

A - Drug Name

isatuximab

COMMON TRADE NAME(S): Sarclisa®

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B - Mechanism of Action and Pharmacokinetics

Isatuximab is a monoclonal antibody derived from IgG1. It targets CD38, a transmembrane glycoprotein expressed in hematopoietic and tumor cells, including multiple myeloma cells. After binding to a specific extracellular epitope of CD38, isatuximab induces cell death via direct and indirect mechanisms.

Distribution	Isatuximab displays nonlinear pharmacokinetics. Disposition is target-mediated due to its binding to CD38 receptor. AUC increased in a dose proportional manner over the range of 5-20 mg/kg weekly for 4 weeks followed by every 2 weeks. Time to reach steady state 8 weeks (median)
Metabolism	Expected to be metabolized by non-saturable catabolic pathways into small peptides.
Elimination	Clearance decreases over time by 50%, with increasing dose and with multiple doses. Half-life 37 days (terminal)

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C - Indications and Status

Health Canada Approvals:

- Multiple myeloma

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: None

The following adverse events were reported in ≥ 5% of patients with multiple myeloma treated with isatuximab in combination with pomalidomide and dexamethasone in a randomized Phase 3 study. It also includes severe or life-threatening adverse effects from other sources. Adverse effects reported with isatuximab in combination with carfilzomib and dexamethasone are denoted with "^".

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (11%) (including atrial fibrillation) (3% severe)	E
	Heart failure (7%) (4% severe) ^	E
Gastrointestinal	Anorexia, weight loss (10%)	E
	Diarrhea (26%)	E
	Mucositis (7%)	E
	Nausea, vomiting (15%)	E
General	Edema - limbs (13%)	E
	Fatigue (42%) ^	E
Hematological	Myelosuppression ± infection, bleeding (47%) (45% severe) (including PJP, viral reactivation)	E
Hypersensitivity	Anaphylaxis (rare)	E
	Infusion related reaction (38%) (3% severe)	I E

Metabolic / Endocrine	Tumor lysis syndrome (rare)	E
Musculoskeletal	Musculoskeletal pain (9%)	E
Neoplastic	Secondary malignancy (4%)	E D L
Nervous System	Dizziness (5%)	E
	Headache (10%)	E
	Tremor (8%)	E
Respiratory	Dyspnea (15%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for isatuximab include myelosuppression ± infection, bleeding, fatigue, infusion related reaction, diarrhea, dyspnea, nausea, vomiting, and edema.

Infusion reactions (IRs) occurred mostly with the first infusion and resolved on the same day. The median time to infusion interruption was 55 minutes.

Cardiac arrhythmias, including atrial fibrillation, were reported with isatuximab in combination with pomalidomide and dexamethasone. Most patients had pre-existing cardiovascular disorders. In patients receiving isatuximab in combination with carfilzomib and dexamethasone, **heart failure** (including fatal events) was reported.

In clinical trials, **herpes zoster reactivation** was reported.

Secondary malignancies (skin carcinoma, breast angiosarcoma, other solid tumours and MDS) were reported in clinical trials with an increased incidence in patients treated with isatuximab-containing regimens compared to the comparator group.

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Isatuximab can interfere with cross-matching for blood transfusions; type and screen and RBC genotyping tests should be done before starting this drug.

Consider antiviral prophylaxis for herpes zoster reactivation.

Pre-medications (prophylaxis for infusion reaction):

To be given 15-60 minutes prior to infusion:

- Dexamethasone IV/PO*^
- Acetaminophen 650-1000 mg PO (or equivalent)
- Diphenhydramine 25-50 mg IV/PO (or equivalent)†
- H2 antagonist

*When dexamethasone is part of isatuximab combination therapy, the treatment dose will serve as pre-medication on infusion days. Refer to the related regimen monograph for dosing information.

^Give dexamethasone IV on the days of isatuximab and/or carfilzomib administration and PO on the other days. (based on isatuximab product monograph)

†IV preferred for at least the first 4 infusions.

Adults:

Refer to the product monograph or related regimen monographs for details.

Combination therapy

Cycle 1:

Intravenous: 10 mg/kg Days 1, 8, 15 and 22; q28 days

Cycles 2 and beyond:

Intravenous: 10 mg/kg Days 1 and 15; q28 days

Dosage with Toxicity:

Dose reductions are not recommended for isatuximab. Doses may be delayed or discontinued in case of neutropenia or IRs.

Toxicity	Severity	Action
Neutropenia	Grade 3 or 4	• Hold until improves to ANC $\geq$ 1 x 10^9/L. • Consider use of colony-stimulating factors (e.g., G-CSF) according to local guidelines.

Management of Infusion-related Reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1	• Continue or stop the infusion. • Monitor the symptoms closely.	• No specific recommendations available.
2	• Stop the infusion. • Manage the symptoms.* **Restart:** • Do not restart if symptoms do not resolve rapidly or do not improve to ≤ Grade 1. • After symptom resolution (≤ Grade 1), restart at 50% of the initial infusion rate ± pre-medications. • If no reaction occurs after 30 minutes, may escalate to initial rate, then incrementally. Refer to Administration section for infusion rates table.	• Discontinue permanently (do not rechallenge) if previously interrupted dose was not restarted.
3 or 4	• Stop treatment. • Aggressively manage symptoms.*	• Discontinue permanently (do not re-challenge).

*Give diphenhydramine 25 mg IV (or equivalent) and/or methylprednisolone 100 mg IV (or equivalent) and/or epinephrine (for Gr. 3-4) as needed to manage symptoms.

Dosage with Hepatic Impairment:

Hepatic Impairment	Isatuximab Dose
Mild (total bilirubin 1 to 1.5 times ULN or AST > ULN)	No dose adjustment necessary
Moderate (total bilirubin >1.5 to 3 times ULN and any AST)	No data
Severe (total bilirubin >3 times ULN and any AST)	

Dosage with Renal Impairment:

No dose adjustment is recommended for renal impairment.

Dosage in the elderly:

No dose adjustments necessary. No overall differences in safety and efficacy were observed between younger and older patients (≥ 65 years).

Children:

Isatuximab was not studied in children under 18 years of age.

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F - Administration Guidelines

- Refer to Infusion Rate table below for initial and subsequent infusion rates.
- Dilute with 250 mL of NS or D5W.
- 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).
- Mix by gently inverting the bag. Do not shake.
- Administer by IV 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).
- Do not infuse concomitantly in the same IV line with other agents.
- When given in combination with carfilzomib or pomalidomide, administer dexamethasone first, followed by isatuximab, then carfilzomib or pomalidomide.
- Store unopened vials between 2 to 8°C (36°F to 46°F). Protect from light.

Infusion Rate

Isatuximab should be administered at the initial infusion rate with incremental escalation as described below. Infusion rate escalations should only be considered in the absence of infusion-related reactions (IRs).

	Dilution Volume	Initial Rate	Absence of IRs	Rate Escalation	Maximum Rate
1st Infusion	250 mL	25 mL/hr	For 60 min	25 mL/hr q30 min	150 mL/hr
2nd Infusion	250 mL	50 mL/hr	For 30 min	50 mL/hr for 30 min, then ↑ by 100 mL/hr	200 mL/hr
Subsequent Infusions	250 mL	200 mL/hr	-	-	200 mL/hr

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any of its components.

Other Warnings/Precautions:

- Patients with primary refractory disease, patients who progressed or were refractory to anti-CD38 treatment were excluded from clinical trials.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unknown
- Fetotoxicity: Probable
  Isatuximab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **5 months** after the last dose.
- Breastfeeding: Not recommended
  It is not known whether isatuximab is excreted into breastmilk. Human IgG is excreted in breast milk.
- Fertility effects: Unknown

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H - Interactions

- Isatuximab interferes with the indirect antiglobulin (Coombs) test by binding to CD38 on RBCs. Patient's blood should be typed and screened, and RBC genotyped prior to initiating treatment. Notify blood transfusion centres of this in the event of a planned transfusion and educate patients.

- Isatuximab may interfere with the serum protein electrophoreses (SPE) and immunofixation (IFE) assays used to monitor M-protein. This can impact the monitoring of response and disease progression in some patients with IgG kappa myeloma protein.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle (consider more frequent monitoring in the first cycle)
Blood type and screen, and RBC genotype	Before starting isatuximab. In the event of a planned transfusion, notify blood transfusion centres.
Electrolytes, renal function tests	Baseline and before each cycle
Liver function tests	Baseline and before each cycle
Clinical toxicity assessment for infusion-related reactions, hypersensitivity, infection (including viral reactivation), secondary malignancies, GI, and cardiac effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Isatuximab and Carfilzomib - In Combination with Dexamethasone for Relapsed or Refractory Multiple Myeloma
- Isatuximab - In Combination with Pomalidomide and Dexamethasone for Relapsed or Refractory Multiple Myeloma

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K - References

Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019 Dec 7;394(10214):2096-2107.

BC Cancer Agency. BC Cancer Extravasation Hazard Table. March 2023.

Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet 2021; 397: 2361–71.

National Comprehensive Cancer Network. Antiemesis: NCCN Guidelines Version 1.2023.

Prescribing information: SARCLISA® (isatuximab-irfc). Sanofi-aventis U.S. LLC. July 2022.

Product monograph: Sarclisa® (Isatuximab). Sanofi-aventis Canada Inc. January 12, 2024.

Xia S, Gong H, Zhao Y, et al. Tumor Lysis Syndrome Associated with Monoclonal Antibodies in Patients with Multiple Myeloma: A Pharmacovigilance Study Based on the FAERS Database. Clin Pharmacol Ther. 2023 Jul;114(1):211-219.

February 2024 Updated Interactions and Monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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