

DRUG NAME: Isatuximab

SYNONYM(S): SAR-650984¹

COMMON TRADE NAME(S): SARCLISA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Isatuximab is a chimeric IgG1-derived monoclonal antibody that targets CD38, a transmembrane glycoprotein expressed in hematological malignancies. By binding to a specific extracellular epitope of CD38, isatuximab triggers several mechanisms leading to the death of CD38-expressing tumours. Isatuximab's direct and indirect antitumour activity includes: activation of antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement dependent cytotoxicity, induction of apoptosis, inhibition of ADP-ribosyl cyclase activity, activation of natural killer cells, and suppression of T-regulatory cells.^{2,3}

PHARMACOKINETICS:

Distribution	median time to reach steady state = 8 weeks	
	cross blood brain barrier?	no information found
	volume of distribution	8.13 L
	plasma protein binding	no information found
Metabolism	expected to be metabolized into small peptides by catabolic pathways	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	clearance decreases with increasing dose and multiple doses	
	urine	no information found
	feces	no information found
	terminal half life	37 days
	clearance	0.00840 L/h
Sex	no clinically meaningful effect	
Elderly	no clinically meaningful effect	
Ethnicity	no clinically meaningful effect	

Adapted from standard reference^{2,3} unless specified otherwise.

USES:

Primary uses:

*Multiple myeloma

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- **premedication** with antihistamine, H₂ antagonist or PPI, antipyretic, and corticosteroid is recommended to prevent/minimize infusion-related reactions^{2,3}
- isatuximab interferes with **cross-matching** and **red blood cell antibody screening**; if possible, perform blood type and screening tests prior to initiating treatment^{2,3}

Carcinogenicity: No carcinogenicity studies have been conducted. Secondary primary malignancies consisting of squamous cell carcinoma of skin, breast angiosarcoma and myelodysplastic syndrome have been reported in patients treated with isatuximab.^{2,3}

Mutagenicity: no information found

Fertility: no information found

Pregnancy: Isatuximab has not been studied in pregnant women or study animals. Human IgG1 is known to cross the placental barrier; therefore, as an IgG1-derived antibody, isatuximab is expected to be transmitted from mother to fetus. Based on its mechanism of action, exposure to isatuximab may cause fetal harm (e.g., immune cell depletion, neurologic defects, decreased bone density, and metabolic disorders). Women of childbearing potential should use effective contraception during treatment and for at least 5 months following the last dose.^{2,3}

Breastfeeding is not recommended due to the potential secretion into breast milk. Human IgG is known to be present in human breast milk.^{2,3}

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.^{4,5} **Incidence data in the Side Effect table is only based on combination therapy with pomalidomide and dexamethasone.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood and lymphatic system/ febrile neutropenia	<i>anemia</i> (99%, severe 28-32%)
	<i>febrile neutropenia</i> (12%)
	lymphopenia (92-93%, severe 44-55%)
	<i>neutropenia</i> (47-96%, severe 45-85%); see paragraph following Side Effects table
	<i>thrombocytopenia</i> (80-84%, severe 25-30%)
cardiac	arrhythmia (11%, severe 3%)
	atrial fibrillation (5%, severe 2%)
eye	blurred vision (<5%)
	cataract (3%) ⁶
gastrointestinal	abdominal distention (<5%)
	<i>emetogenic potential: low</i> ⁷

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	diarrhea (26%, severe 2%)
	gastroesophageal reflux disease (<5%)
	nausea (15%)
	stomatitis (7%, severe <1%)
	upper abdominal pain (<5%)
	vomiting (12%, severe 1%)
general disorders and administration site conditions	extravasation hazard : none ⁸
	peripheral edema (13%, severe <1%)
	pyrexia (<5%)
immune system	cytokine release syndrome (<5%)
infections and infestations	bronchitis (24%, severe 3%)
	herpes viral infection (10%, severe <1%)
	influenza (<5%)
	nasopharyngitis (9%)
	<i>Pneumocystis jirovecii</i> pneumonia (<5%)
	pneumonia (31%, severe 25-26%); fatal events reported
	sepsis (<5%)
	upper respiratory tract infection (28%, severe 3-7%)
injury, poisoning, and procedural complications	infusion-related reaction (38-47%, severe 3-5%); see paragraph following Side Effects table
investigations	gamma-glutamyltransferase increase (<5%)
	weight decrease (7%)
metabolism and nutrition	appetite decrease (10%, severe 1%)
	diabetes mellitus (<5%)
	hyperglycemia (<5%)
musculoskeletal and connective tissue	arthralgia (<5%)
	bone pain (8%, severe <1%)
	joint swelling (<5%)
	muscular weakness (7%, severe <1%)
	musculoskeletal chest pain (9%)
	myalgia (7%)
neoplasms	second primary malignancy (3-4%); includes squamous cell carcinoma (3%), breast angiosarcoma (<1%) and myelodysplastic syndrome (<1%)
nervous system	dizziness (5%)
	headache (10%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
	lethargy (<5%)
	tremor (8%, severe 2%)
psychiatric	agitation (<5%)
	anxiety (<5%)
	confusional state (<5%)
	restlessness (<5%)
renal and urinary	urinary incontinence (<5%)
respiratory, thoracic and mediastinal	dyspnea (15-17%, severe 4-5%)
	hiccups (<5%)
	pulmonary embolism (2%) ⁶
vascular	hot flashes (<5%)
	hypertension (<5%)

Adapted from standard reference^{2,3} unless specified otherwise.

Infusion-related reactions are reported in up to ~50% of patients. The majority of cases (98%) occur during the first infusion and resolve on the same day. Median time to infusion interruption is 55 minutes. Dyspnea, cough, chills, nasal congestion and nausea are commonly reported. Severe reactions with hypertension and bronchospasm may also occur. To minimize the risk and severity of reaction, premedication with an antipyretic, H₂ antagonist or PPI, antihistamine, and corticosteroid is recommended. When dexamethasone is prescribed as part of combination therapy, additional dexamethasone premedication may not be required. Permanently discontinue isatuximab if a Grade 3 or higher infusion-related reaction occurs, or if symptoms do not improve or recur after infusion interruption.¹⁻⁵ For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX [Management of Infusion-Related Reactions to Systemic Therapy Agents](#).

Neutropenia is frequently reported. Severe, life-threatening, and fatal infections associated with neutropenia have occurred, including pneumonia, and infections of the upper and lower respiratory tract. Patients with neutropenia should be closely monitored for signs of infection and promptly treated. Isatuximab dose reduction is not required; however, treatment interruption may be required to allow for neutrophil count recovery. Supportive care with growth factors may also be necessary.^{2,3}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
serological testing (indirect antiglobulin test) ^{2,3}	false positive reaction in Coombs test, antibody screening test, antibody identification panel, and antihuman globulin cross-matches	isatuximab binds to CD38 on red blood cells	type and screen patients prior to initiating treatment; if emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given

AGENT	EFFECT	MECHANISM	MANAGEMENT
serum protein electrophoresis (SPE) and immunofixation (IFE) assays ^{2,3}	false positive SPE and IFE assay results in patients with IgG kappa M-protein	isatuximab is detected on SPE and IFE assays used for monitoring endogenous M-protein	additional tests may be required to evaluate response

SUPPLY AND STORAGE:

Injection: sanofi-aventis Canada Inc. supplies isatuximab as 100 mg and 500 mg single-use (no preservative) vials in a concentration of 20 mg/mL. Refrigerate. Do not shake. Protect from light.²

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold, italics***

Subcutaneous	no information found																				
Intramuscular	no information found																				
Direct intravenous	no information found																				
Intermittent infusion	<p>refer to protocol by which patient is being treated; administer with a 0.22 micron in-line filter^{2,3}</p> <p>in the absence of other guidelines, the following incremental infusion rate may be used:²</p> <table border="1"> <thead> <tr> <th></th> <th>Dilution Volume</th> <th>Initial Rate (mL/h)</th> <th>Rate Increment</th> <th>Max Rate (mL/h)</th> </tr> </thead> <tbody> <tr> <td>first infusion</td> <td>250 mL</td> <td>25</td> <td>25 mL/h every 30 minutes^a</td> <td>150</td> </tr> <tr> <td>second infusion</td> <td>250 mL</td> <td>50</td> <td>50 mL/h for 30 minutes, then increase by 100 mL/h every 30 minutes^b</td> <td>200</td> </tr> <tr> <td>subsequent infusions</td> <td>250 mL</td> <td>200</td> <td>--</td> <td>200</td> </tr> </tbody> </table> <p>^aescalate only in the absence of infusion reaction for 60 minutes at initial rate ^bescalate only in the absence of infusion reaction for 30 minutes at initial rate</p>		Dilution Volume	Initial Rate (mL/h)	Rate Increment	Max Rate (mL/h)	first infusion	250 mL	25	25 mL/h every 30 minutes ^a	150	second infusion	250 mL	50	50 mL/h for 30 minutes, then increase by 100 mL/h every 30 minutes ^b	200	subsequent infusions	250 mL	200	--	200
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subsequent infusions	250 mL	200	--	200																	
Continuous infusion	no information found																				
Intraperitoneal	no information found																				
Intrapleural	no information found																				

BC Cancer administration guideline noted in ***bold, italics***

Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

<i>Intravenous:</i>	<p>Cycle Length: 4 weeks:²</p> <p>Cycle 1: 10 mg/kg IV for one dose on days 1, 8, 15, and 22 (total dose per cycle 40 mg/kg)</p> <p>Cycle 2 onward: 10 mg/kg IV for one dose on day 1 and 15 (total dose per cycle 20 mg/kg)</p> <p>Dose reductions are not recommended</p>
<i>Concurrent radiation:</i>	no information found
<i>Dosage in myelosuppression:</i>	refer to protocol by which patient is being treated; dose reduction is not recommended, however, dose delay may be required to allow recovery from hematological toxicity ^{2,3}
<i>Dosage in renal failure:</i>	no adjustment required ²
	<p>calculated creatinine clearance = $\frac{N * (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$</p> <p>* For males N=1.23; for females N=1.04</p>
<i>Dosage in hepatic failure:</i>	mild impairment: no adjustment required ² moderate/severe impairment: no information found
<i>Dosage in dialysis:</i>	no information found
<u>Children:</u>	safety and efficacy not established

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