# DRUG NAME: Isatuximab

**SYNONYM(S):** SAR-650984 [1]

**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

***Other uses:***

*Health Canada approved indication



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## SPECIAL PRECAUTIONS:

***Caution:***
- ***premedication*** with antihistamine, $H_2$ 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]
- antiviral prophylaxis may be required for prevention of ***herpes zoster reactivation*** [4]

***Carcinogenicity:*** No carcinogenicity studies have been conducted. Second 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 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. The effect of exposure of the breastfed infant via the gastrointestinal tract is unclear. [4]

## 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. [5,6] **Incidence data in the Side Effect table is only based on combination therapy. Monotherapy data is not available.**

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia | ***anemia*** (99%, severe 22-32%) [4] |
| | ***febrile*** **neutropenia** (12%) |
| | lymphopenia (92-94%, severe 44-69%) [4] |
| | ***neutropenia*** (47-96%, severe 20-85%) [4]; see paragraph following **Side Effects** table |
| | ***thrombocytopenia*** (80-94%, severe 25-31%) [4] |
| cardiac | arrhythmia (11%, severe 3%); mostly in patients with pre-existing cardiac disorders [4] |
| | atrial fibrillation (5%, severe 2%) |
| | cardiac failure [4] (7%, severe 4%); fatal events reported |
| eye | blurred vision (<5%) |
| | cataract (3%) [7] |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| gastrointestinal | abdominal distention (<5%) |
| | *emetogenic potential:* low [8] |
| | ***diarrhea*** (26-36%, severe 2%) |
| | gastroesophageal reflux disease (<5%) |
| | nausea (15%) |
| | stomatitis (7%, severe <1%) |
| | upper abdominal pain (<5%) |
| | vomiting (12-15%, severe 1%) |
| general disorders and administration site conditions | *extravasation hazard:* none [9] |
| | fatigue [4] (42%, severe 5%) |
| | peripheral edema (13%, severe <1%) |
| | pyrexia (<5%) |
| immune system | anaphylactic reactions [4] (<1%) |
| | cytokine release syndrome (<5%) |
| infections and infestations | bronchitis (24%, severe 3%) [4] |
| | herpes viral infection (2-10%, severe <1%) [4] |
| | influenza (<5%) |
| | nasopharyngitis (9%) |
| | *Pneumocystis jirovecii* pneumonia (<5%) |
| | ***pneumonia*** (31-36%, severe 22-26%) [4]; fatal events reported |
| | sepsis (<5%) |
| | ***upper respiratory tract infection*** (28-67%, severe 3-9%) [4] |
| injury, poisoning, and procedural complications | ***infusion-related reaction*** (38-47%, severe 1-5%); 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%) |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| neoplasms | second primary malignancy (3-4%); includes squamous cell carcinoma (3%), breast angiosarcoma (<1%) and myelodysplastic syndrome (<1%) |
| nervous system | dizziness (5%) |
| | headache (10%) |
| | lethargy (<5%) |
| | tremour (8%, severe 2%) |
| psychiatric | agitation (<5%) |
| | anxiety (<5%) |
| | confusional state (<5%) |
| | restlessness (<5%) |
| renal and urinary | urinary incontinence (<5%) |
| respiratory, thoracic and mediastinal | cough [4] (23%) |
| | dyspnea (15-29%, severe 4-5%) [4] |
| | hiccups (<5%) |
| | pulmonary embolism (2%) [7] |
| vascular | hot flashes (<5%) |
| | hypertension (37%, severe 21%) [4] |

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, $H_2$ antagonist or PPI, antihistamine, and corticosteroid is recommended. When dexamethasone is prescribed as part of combination therapy, additional dexamethasone premedication may not be required. [1-3,5,6] Consider permanently discontinuing isatuximab for grade 3 or higher infusion-related reactions or if symptoms do not improve or recur after infusion interruption. [4] 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]



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## 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 |
| 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 (preservative free) 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 | over 0.5-10 h[4,10-13]; refer to protocol by which patient is being treated |
| | administer with an in-line filter [4] (e.g., 0.2 micron) |



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

| | |
|---|---|
| | In the absence of other guidelines, the following incremental infusion rate may be used: [4]<br><br>**first infusion**: Dilution Volume 250 mL; Initial Rate 25 mL/h; Rate Increment 25 mL/h every 30 min[a]; Max Rate 150 mL/h<br>**second infusion**: Dilution Volume 250 mL; Initial Rate 50 mL/h; Rate Increment 50 mL/h for 30 min, then increase by 100 mL/h every 30 min[b]; Max Rate 200 mL/h<br>**subsequent infusions**: Dilution Volume 250 mL; Initial Rate 200 mL/h; Rate Increment --; Max Rate 200 mL/h<br><br>[a]escalate only in the absence of infusion reaction for 60 min at initial rate<br>[b]escalate only in the absence of infusion reaction for 30 min at initial rate |
| Continuous infusion | no information found |
| Intraperitoneal | no information found |
| Intrapleural | no information found |
| 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***

| | | |
|---|---|---|
| *Intravenous:* | Cycle Length:<br>***4 weeks*** [4,12,13]: | Cycle 1:<br>***10 mg/kg IV for one dose on days 1, 8, 15, and 22***<br>(total dose per cycle 40 mg/kg)<br><br>Cycle 2 onward:<br>***10 mg/kg IV for one dose on day 1 and 15***<br>(total dose per cycle 20 mg/kg)<br><br>Dose reductions are not recommended |
| *Concurrent radiation:* | no information found | |
| *Dosage in myelosuppression:* | refer to protocol by which patient is being treated;<br>dose reduction is not recommended, however, dose delay may be required to allow recovery from hematological toxicity [4] | |
| *Dosage in renal failure:* | no adjustment required [4] | |



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

| | |
|---|---|
| *Dosage in hepatic failure:* | Cycle Length:<br>mild impairment: no adjustment required [4]<br>moderate/severe impairment: no information found |
| *Dosage in dialysis:* | no information found |

***Children:*** safety and efficacy not established

## REFERENCES:


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