Drug Monograph

A - Drug Name

siltuximab

COMMON TRADE NAME(S): Sylvant®

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B - Mechanism of Action and Pharmacokinetics

Siltuximab is a chimeric monoclonal antibody to IL-6 that prevents binding of IL-6 to both soluble and membrane-bound IL-6 receptors, inhibiting formation of a signalling complex with gp130 on the cell surface. IL-6 is a pro-inflammatory cytokine produced by many cell types, including malignant cells.

Distribution	Limited extravascular tissue distribution	
Metabolism	Antibodies are degraded into small peptides and amino acids via catabolism.	
Elimination	No formal studies have been conducted.	
	Half-life	16 days (following single-dose)

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C - Indications and Status

Health Canada Approvals:

- Multicentric Castleman's disease (MCD)

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

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

Adverse effects reported were mainly from a pooled analysis of the randomized, phase 2 study and the phase 1 study comparing siltuximab to placebo, where the incidence was higher than placebo.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (13%)	E
	Hypotension (4%)	E
Dermatological	Rash (23%)	E
	Skin hyperpigmentation (6%)	E
Gastrointestinal	Abdominal pain (16%)	E
	Constipation (12%)	E
	Diarrhea (26%)	E
	Gastroesophageal reflux disease (5%)	E
	GI perforation (rare)	E
	Mucositis (4%)	E
	Nausea, vomiting (18%)	E
General	Edema - limbs (26%)	E
	Fever (11%)	E
Hematological	Myelosuppression ± infection, bleeding (13%) (including atypical infection; may be severe)	E
	Other (1.2%) (polycythemia)	E

Hepatobiliary	↑ LFTs (10%)	E
Hypersensitivity	Hypersensitivity (1.5%) (severe)	I E
Infection	Infection (38%) (including atypical)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (13%) (decreased K, Ca, Mg, Na)	E
	↑ Cholesterol (9%)	E
	Hyperuricemia (15%)	E
	↑ Triglycerides (13%)	E
Musculoskeletal	Musculoskeletal pain (12%)	E
Nervous System	Dizziness (9%)	E
	Headache (13%)	E
	Peripheral neuropathy (22%)	E
	Syncope (4%)	E
Ophthalmic	Blurred vision (6%)	E
Renal	Creatinine increased (12%)	E
Vascular	Hot flashes (17%) (night sweats)	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 siltuximab include infection, diarrhea, edema - limbs, rash, peripheral neuropathy, nausea, vomiting, hot flashes, abdominal pain, hyperuricemia and ↑ triglycerides.

Serious **infections** have been reported with siltuximab, including pneumonia and sepsis. The drug may mask signs and symptoms of acute inflammation, including fever and elevated C-reactive protein. Patients should be monitored closely and infections should be treated promptly.

Infusion-related reactions were reported in 7.5% of patients in the clinical study. Mild to moderate reactions may improve by slowing or stopping the infusion temporarily. Consider pre-medication with antihistamines, acetaminophen and corticosteroids prior to the next infusion.

GI perforation was reported in other clinical trials, but not in MCD trials. Use with caution in patients at risk.

Hypertriglyceridemia and **hypercholesterolemia** have been reported. Patients who develop these should be managed according to clinical guidelines.

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E - Dosing

Refer to protocol by which 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.

Patients should be tested to confirm they are not HIV or HHV-8 positive before starting treatment. Infections, including localized ones should be treated prior to starting siltuximab.

Do not initiate treatment until ANC ≥ 1.0 x 10^9/L, platelets ≥ 75 x 10^9/L and hemoglobin is < 170 g/L.

Adults:

Intravenous: 11 mg/kg over 1 hour Day 1, repeat every 21 days

Dosage with Toxicity:

Dose reduction is not recommended. Doses may be delayed for toxicity for up to 3 weeks (van Rhee 2014).

Toxicity	Action
ANC < 1 x 10^9/L or platelets < 50 x 10^9/L	Hold* until recovery
Severe infection or non-hematologic toxicity	Hold* until recovery
Mild to moderate infusion-related reaction	Slow or hold infusion until recovery and treat. Consider pre-medication** prior to the next infusion.
Severe infusion-related reaction, anaphylaxis or cytokine-release syndrome	Discontinue and manage appropriately.

*Do not retreat until ANC ≥ 1 x 10^9/L, platelets ≥ 50 x 10^9/L, non-hematologic toxicity ≤ grade 2 or baseline

**Antihistamine, acetaminophen and corticosteroids

Dosage with Hepatic Impairment:

No formal studies have been conducted. Mild to moderate hepatic impairment had no significant effect on siltuximab pharmacokinetics.

Dosage with Renal Impairment:

No formal studies have been conducted. Mild to moderate renal impairment had no significant effect on siltuximab pharmacokinetics.

Dosage in the elderly:

No major age-related changes in pharmacokinetics or safety were observed in clinical studies, but these did not include sufficient numbers of patients aged 65 and older to determine the effect of age on efficacy.

Dosage based on gender:

No clinical effect on drug clearance was observed in population pharmacokinetic analyses.

Dosage based on ethnicity:

No clinical effect on drug clearance was observed in population pharmacokinetic analyses.

Children:

Safety and efficacy have not been established in pediatric patients.

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F - Administration Guidelines

- Reconstitute with sterile water for injection as directed in the product monograph.
- Gently swirl to mix; DO NOT shake or stir vigorously.
- Do not use if visibly opaque particles are present and/or solution is discoloured.
- Dilute reconstituted solution with D5W to the desired concentration.
- Administer diluted solution over 1 hour using administration sets lined with PVC, PU or PE containing a 0.2-micron inline PES filter.
- Diluted solution should be administered within 6 hours of preparation.
- Siltuximab should be refrigerated between 2 to 8^{o}C.
- DO NOT freeze and protect from light.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Live, attenuated vaccines should not be given concurrently or within 4 weeks of starting treatment.
- Clinical studies excluded patients with significant infections, including patients positive for hepatitis B surface antigen. Cases of reactivated hepatitis B have been reported when siltuximab was given with chemotherapy in multiple myeloma patients.
- Use with caution in patients who may be at risk of GI perforation.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Embryotoxicity: Unknown
- Fetotoxicity: Unknown
- Teratogenicity: Unlikely
- Pregnancy:
  Siltuximab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **3 months** after the last dose. As siltuximab can cross the placenta, exposed infants may be at increasd risk of infection; caution is advised in the administration of live vaccines.
- Breastfeeding:
  Breastfeeding is not recommended.
- Fertility effects: Unknown

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H - Interactions

No formal drug interaction studies have been conducted. Binding of siltuximab to IL-6 may increase the metabolism of CYP450 subtrates.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↓ concentration and/or efficacy	↑ metabolism of substrates	Caution with drugs with narrow therapeutic index; monitor closely
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	↓ concentration and/or efficacy	↑ metabolism of substrates	Caution with drugs with narrow therapeutic index; monitor closely
Oral contraceptives	↓ concentration and/or efficacy	↑ metabolism	Caution; consider alternative method of contraception

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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 dose for the first 12 months and every 3 cycles thereafter
Liver and renal function tests	Baseline and as clinically indicated
Blood pressure	Baseline and as clinically indicated
Cholesterol and triglycerides	Baseline and periodic
Clinical toxicity assessment for infection, bleeding, infusion-related reactions, GI 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)

- Siltuximab - Multicentric Castleman's Disease (MCD)

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K - References

Siltuximab product monograph. Janssen Inc. January 6, 2016.

van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2014 Aug;15(9):966-74.

March 2025 Updated Pregnancy/Lactation section

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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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