DRUG NAME: Siltuximab

SYNONYM(S): CNTO 328[1]

COMMON TRADE NAME(S): SYLVANT®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Siltuximab is a human-murine chimeric monoclonal antibody that prevents human interleukin-6 (IL-6) from binding to both soluble and membrane-bound IL-6 receptors. IL-6 is a polyfunctional, pro-inflammatory cytokine produced by a variety of cell types including B and T cells, as well as some malignant cells. IL-6 induces immunoglobulin secretion, initiates hepatic acute phase protein synthesis and stimulates proliferation and differentiation of hematopoietic precursor cells. By blocking the IL-6 mediated signal transduction pathway, siltuximab decreases systemic manifestations of IL-6 overproduction such as inflammation, anemia, cachexia, and plasma cell proliferation. Siltuximab is an immunosuppressive agent.[2-4]

PHARMACOKINETICS:

Distribution	limited extravascular tissue distribution	
	cross blood brain barrier?	no information found
	volume of distribution[5]	4.5 L
	plasma protein binding	no information found
Metabolism	possibly degraded catabolically into small peptides and amino acids	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	with repeat dosing, clearance is time-invariant and there is moderate systemic accumulation	
	urine	no information found
	feces	no information found
	terminal half life	16.3 days
	clearance	3.54 mL/kg/day

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

*Multicentric Castleman's disease

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTION:

Caution:
- ***serious active infection***, including ***localized infection***, should be treated and resolved prior to therapy; siltuximab may mask infection, inflammation, and suppress fever and C-reactive protein[3]
- ***live, attenuated vaccines*** should not be given concurrently or within 4 weeks prior to the first treatment of siltuximab[3]
- reactivation of ***Hepatitis B*** has been reported[3]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***[7]

Special populations:
- ***HIV*** and ***human herpes virus type-8*** positive patients may have a decreased response to siltuximab; studies suggest siltuximab does not bind to virally produced IL-6.[6]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal studies, no histopathological changes were observed in reproductive tissues or effects on male or female fertility.[3]

Pregnancy: Animal studies show that siltuximab crosses the placenta. Serum concentrations were similar in both mother and fetus; however, no maternal and/or fetal toxicities were observed. However, infants born to mothers on siltuximab may have a higher risk of infection; use caution when administering live vaccines in this population. Patients of childbearing potential should use contraception during treatment and for three months following the last dose of siltuximab.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk.[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.[7,8] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	neutropenia (11-14%, severe 5%)
	hemoglobin increase (61%); see paragraph following **Side Effects** table
	thrombocytopenia (9-14%, severe 3%)[3,10]
eye	blurred vision (6%)
gastrointestinal	*emetogenic potential:* low[11]
	abdominal distension (6%)
	abdominal pain (12-16%)[3,10]
	constipation (8-12%)[3,10]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	diarrhea (26-32%)[3,10]
	gastrointestinal perforation (<1%)
	gastroesophageal reflux disease (5%)
	vomiting (18%)
general disorders and administration site conditions	*extravasation hazard:* none[12]
	fatigue (21%)[10]
	localized edema (15-18%, severe 3%)[3]
	peripheral edema (16-26%)[3,10]
immune system (see paragraph following **Side Effects** table)	***anaphylaxis*** (<1-2%, severe 2%)[3,10]
	infusion-related reaction (5-8%)[3,10]
infections and infestations (see paragraph following **Side Effects** table)	lower respiratory tract infection (8%)[10]
	nasopharyngitis (12-13%)
	upper respiratory tract infection (26-38%)[3,10]
	urinary tract infection (9%)
investigations	bilirubin increase (5%)
	hypercholesterolemia (4-9%)[3,10]
	polycythemia (severe 1%)[3]
	weight gain (15-19%, severe 3%)[3,10]
metabolism and nutrition	appetite decrease (4%)[10]
	dehydration (4%)[10]
	hypertriglyceridemia (8-13%, severe 3%)[3,10]
	hyperuricemia (11-15%)[3,10]
	hypokalemia (13%)
musculoskeletal and connective tissue	arthralgia (12-21%)[3,10]
	pain in extremity (6-21%)[10]
	muscle weakness (6%)
nervous system	headache (8-13%)[3,10]
renal and urinary	renal impairment (8-12%, severe 3%)[3,10]
respiratory, thoracic and mediastinal	oropharyngeal pain (8-10%)[3,10]
skin and subcutaneous tissue	eczema (4-7%)[3,10]
	night sweats (17%)[3]
	pruritis (28-36%)[3,10]
	psoriasis (4%)[10]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	skin hyperpigmentation (4-6%)[3,10]
	skin rash (28-29%, severe 2%)[3,10]
	xeroderma (4-7%)[3,10]
vascular	***hypertension*** (11-13%, severe 6%)
	hypotension (4-6%, severe 2%)[3,10]

Adapted from standard reference[10] unless specified otherwise.

Siltuximab may indirectly cause ***elevated hemoglobin levels***. Although this is considered a positive outcome following treatment with siltuximab, the drug has been associated with development of secondary polycythemia.[13] IL-6 induces the production of hepcidin, an iron regulatory hormone that contributes to hemoglobin homeostasis. When hepcidin levels are high, serum iron levels fall and an inadequate amount of serum iron is available for developing red blood cells, thus typically leading to anemia. By its mechanism of action, siltuximab will bind to IL-6 and block its effects, causing hepcidin levels to decrease. The sequestered iron will then be released back into the blood, improving the anemia.[2] However, hemoglobin levels of 170 mg/L or greater may require interruption of siltuximab therapy.[3]

Infusion reactions may include back pain, chest pain/discomfort, nausea, vomiting, flushing, erythema and/or palpitations. Mild to moderate infusion reactions may improve by slowing or stopping the infusion temporarily. Following resolution of the reaction, siltuximab may be resumed at a slower infusion rate. Consider pre-medication with antihistamines, acetaminophen, and/or corticosteroids. Permanently discontinue siltuximab for infusion reactions which recur despite premedication and/or rate reduction, as well as severe infusion related reactions, cytokine release syndrome, severe allergic reaction, or anaphylaxis.[3,6,10]

Serious infections, including pneumonia and sepsis, may occur during siltuximab therapy. Temporarily withhold siltuximab until the infection resolves and initiate anti-infective therapy as needed. Siltuximab may be restarted at the same dose after recovery.[3,10]

INTERACTIONS: No known interactions.[3]

Excess IL-6 downregulates the activity of CYP 450 enzymes. By binding to IL-6, siltuximab treatment will normalize CYP450 activity, potentially increasing the metabolism of CYP 450 substrates. Therapeutic effect and toxicity of CYP 450 substrates may be affected. Substrates with a narrow therapeutic index may require additional monitoring, particularly when siltuximab treatment is initiated or discontinued. This effect may also persist several weeks after stopping siltuximab. Clinical significance is unknown.[3]

SUPPLY AND STORAGE:

***Injection*:** Janssen Inc. supplies siltuximab as 100 mg and 400 mg single-use (preservative-free) vials of lyophilized powder for injection. Refrigerate. Do not freeze. Protect from light.[3]

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

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SOLUTION PREPARATION AND COMPATIBILITY:

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Additional information[3]***:***
- allow vial to come to room temperature (~30 minutes) prior to preparation
- lyophilized powder should dissolve in less than 60 minutes
- administer with a 0.2 micron inline filter

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 60 minutes***[3,14]
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 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: 3 weeks[3,14]:	***11 mg/kg IV for one dose on day 1*** (total dose per cycle 11 mg/kg)
Concurrent radiation:	no information found	
Dosage in myelosuppression[3,9]*:*	do NOT dose reduce; modify treatment according to protocol by which patient is being treated	
Dosage in renal failure[5,10]*:*	CrCl >15 mL/min: no dose adjustment required CrCl <15 mL/min: no information found	

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

Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu mol/L}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure[5,10]*:* no initial dose adjustment required for mild to moderate impairment; no information found for severe impairment

Dosage in dialysis: no information found

Children: no information found

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