

DRUG NAME: Tocilizumab

SYNONYM(S): RO4877533¹

COMMON TRADE NAME(S): ACTEMRA®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Tocilizumab is a humanized anti-human IL-6 antibody² that binds specifically to both soluble and membrane-bound IL-6 receptors and inhibits IL-6 mediated signalling through these receptors. Tocilizumab is an immunosuppressant.³

USES:

Primary uses:

Other uses:

Castleman disease^{2,4,5}

Cytokine release syndrome^{6,7}

*Health Canada approved indication

SPECIAL PRECAUTIONS:

- tocilizumab has been associated with **serious infections (bacterial, mycobacterial, viral, fungal, etc.)**; avoid use in patients with active infections (including chronic or localized infections) and use cautiously in patients with a history of serious or opportunistic infections or who have visited areas of endemic infections⁸
- test for active and latent **tuberculosis** prior to treatment with tocilizumab; delay tocilizumab and complete treatment for TB prior to using tocilizumab⁸
- **screen** for viral hepatitis prior to treatment as **reactivation of hepatitis B and C** has been reported⁸
- exacerbation of **herpes zoster** may occur with tocilizumab⁸
- patients with a history of **gastrointestinal ulceration and diverticulitis** may be at higher risk for gastrointestinal perforation⁸
- **multiple sclerosis** and chronic inflammatory **demyelinating polyneuropathy** have been reported with tocilizumab; use cautiously in patients with preexisting or recent onset demyelinating disorders as the impact is unknown⁸
- avoid live and live attenuated **vaccines** during treatment with tocilizumab; complete immunizations prior to treatment⁸
- serious drug-induced **liver injury** has been reported; avoid tocilizumab in patients with active hepatic disease or liver impairment⁹

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. When placebo-controlled trials are available, adverse events are included if the incidence is $\geq 5\%$ higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood and lymphatic system/ febrile neutropenia	anemia (1-2%)
	leukopenia (1-4%); transient, mild ¹⁰
	neutropenia (1-4%)
	thrombocytopenia (1-2%)
cardiac	hypertension (5-12%)
gastrointestinal	<i>emetogenic potential</i> : minimal/rare ¹¹
	gastritis (1%)
	gastrointestinal perforation (<1%)
	nausea (3-13%)
	oral ulceration (2%)
	upper abdominal pain (2%)
	vomiting (1-10%)
general disorders and administration site conditions	<i>extravasation hazard</i> : none ¹²
	infusion reactions (4-23%, severe <1%); see paragraph following Side Effects table
	injection site reactions (2-4%)
hepatobiliary	hepatotoxicity ^{9,13} (<1%); see paragraph following Side Effects table
immune system	hypersensitivity reactions , including anaphylaxis (1-3%) ^{8,14} ; see paragraph following Side Effects table
	secondary malignancies (2%)
infections and infestations	candidiasis (1-3%)
	cellulitis (1-3%)
	diverticulitis (<1%)
	fungal infection (1-4%)
	herpes simplex (1-4%)
	herpes zoster (2-5%)
	mycoplasmal pneumonia (3%)
	pneumonia (1-5%)
	sepsis (1%)
	upper respiratory tract infection (2-14%)
urinary tract infection (2-10%)	
investigations	ALT increase (1-5%) ¹⁵
	AST increase (1-4%) ¹⁵
	dyslipidemia (2%)
	hypercholesterolemia (2-3%); occurs within 6 weeks, then may stabilize; responds to lipid lowering agents

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	hyperlipidemia (1-2%); occurs within 6 weeks, then may stabilize
	hypertriglyceridemia (2%); occurs within 6 weeks, then may stabilize
nervous system	dizziness (3%)
	headache (7%)
	multiple sclerosis, chronic inflammatory demyelinating polyneuropathy (<1%)
skin and subcutaneous tissue	rash (2%)

Adapted from standard reference^{3,8} unless specified otherwise.

Tocilizumab is known to cause transient or intermittent mild to moderate elevation of **hepatic transaminases**. Most elevations are single occurrences. Events occur with increased frequency when tocilizumab is used in combination with other potentially hepatotoxic drugs. Rarely, moderate to severe **liver injury** (e.g., acute liver failure, hepatic cirrhosis, hepatitis, etc.) has been reported. In some cases, patients have required liver transplantation following acute liver failure. Dose adjustment, treatment delay, or permanent discontinuation of tocilizumab may be required for persistent transaminase elevations. Avoid tocilizumab in patients with active hepatic disease or signs of hepatic impairment. Monitor transaminases and other liver parameters regularly during treatment.^{9,13,15,16}

Infusion-related reactions may occur during the infusion or within 24 hours of the start of the infusion. Reactions are usually transient and mild. Hyper- or hypotension, headache, nausea, rash, pruritus, and urticaria are the most frequently reported symptoms. These events are not usually treatment limiting and premedication is not required.^{8,10}

Serious **hypersensitivity reactions**, including anaphylaxis and anaphylactoid reactions, have been rarely reported and are sometimes fatal. Serious reactions have been reported both with and without premedication, as well as with no prior history of hypersensitivity reactions. The majority of cases occur between the second and fourth infusions, but hypersensitivity reactions have also been observed as early as the first infusion and up to the twentieth. Following a reaction, immediately stop tocilizumab infusion. Patients with clinically significant hypersensitivity to tocilizumab should not be rechallenged.⁸

SUPPLY AND STORAGE:

Injection: F. Hoffmann-La Roche Ltd. supplies tocilizumab as 80 mg, 200 mg, and 400 mg ready-to-use single-use (preservative free) vials in a concentration of 20 mg/mL. Refrigerate. Protect from light in original packaging.^{4,8}

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](#).

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	do NOT use ⁸
<i>Intermittent infusion</i>	<i>over 60 minutes^{4,8}</i>
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***

<i>Intravenous:</i>	Cycle Length:	<i>2 weeks^{2,4,10,17}</i>	<i>4-8 mg/kg IV for 1 dose on day 1</i>
			Max dose = 800 mg per infusion ⁸
	n/a ^{6,7} :		8 mg/kg IV q8h prn (up to 4 doses total)
			Max dose = 800 mg per infusion

REFERENCES:

- Hoffmann-La Roche Ltd. Tocilizumab investigator's brochure addendum to version 11. April 2010.
- Nishimoto N, Terao K, Mima T, et al. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood* 2008;112(10):3959-3964.
- Genentech Inc. ACTEMRA® full prescribing information. South San Francisco, California; January 2010.
- Hoffmann-La Roche Ltd. Provision of tocilizumab for a patient with multicentric Castleman's Disease: guidelines for compassionate use. May 2010.
- Muskardin TW, Peterson BA, Molitor JA. Castleman disease and associated autoimmune disease. *Curr Opin Rheumatol* 2012;24(1):76-83.
- Genentech Inc. ACTEMRA® full prescribing information. South San Francisco, California; December 2018.
- Shimabukuro-Vornhagen A, Godel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer* 2018;6(56):1-14.
- Hoffmann-La Roche Limited. ACTEMRA® product monograph. Mississauga, Ontario; 27 October 2017.
- Health Canada. Recalls and Safety Alerts: Important safety information on ACTEMRA® (tocilizumab) - risk of hepatotoxicity. 21 May 2019. Available at: <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>. Accessed 11 June 2019.

10. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood* 2005;106(8):2627-2632.
11. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 Dec 2018.
12. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; January 2016.
13. Genovese MC, Kremer JM, van Vollenhoven RF, et al. Transaminase levels and hepatic events during tocilizumab treatment: pooled analysis of long-term clinical trial safety data in rheumatoid arthritis. *Arth & Rheumatol* 2017;69(9):1751-1761.
14. Hoffmann-La Roche Limited. Health Canada Endorsed Important Safety Information on ACTEMRA® (tocilizumab) - Risk of fatal anaphylaxis. Health Canada, 13 September 2010. Available at: <http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2010/14586a-eng.php>. Accessed 26 February 2019.
15. Hoffmann-La Roche Limited. ACTEMRA® product monograph. Mississauga, Ontario; 9 May 2019.
16. Jan Campbell, Director Medical Affairs. Important Safety Information on ACTEMRA® (tocilizumab) - A new important identified risk: hepatotoxicity. Roche Products (New Zealand) Limited, 7 May 2019. Available at: <https://medsafe.govt.nz/safety/DHCPLetters/ActemraMay2019.pdf>. Accessed 11 June 2019.
17. Hoffmann-La Roche Ltd. Tocilizumab investigator's brochure version 11. September 2009.