Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

alemtuzumab

COMMON TRADE NAME(S): MabCampath®

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B - Mechanism of Action and Pharmacokinetics

Alemtuzumab is a monoclonal antibody that binds to the CD52 antigen on the surface of malignant lymphocytes and induces cell lysis. The CD52 antigen is present on the surface of essentially all B and T lymphocytes, most monocytes, macrophages, NK cells, and some granulocytes and normal bone marrow cells. Alemtuzumab was approved for use based on objective responses and progression-free survival. No data is available from randomized controlled trials regarding improved survival or quality of life.

Absorption	Oral: no	
Distribution	Alemtuzumab displays non-linear elimination kinetics. Systemic clearance decreases with repeated administration due to decreased receptor-mediated clearance (i.e. loss of CD52 receptors in the periphery).	
	Cross blood brain barrier?	No information found
	PPB	No information found
Metabolism	Active metabolites	No information found
	Inactive metabolites	No information found
Elimination	Half-life	11 hours (range: 2-32 hours) after the first 30 mg dose and 6 days (range: 1-14 days) after the last 30 mg dose

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C - Indications and Status

Health Canada Approvals:

- Treatment of B cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.
- Treatment of patients with previously untreated progressive B-CLL. The effectiveness is based on progression-free survival, complete response, and overall response rates. No current data available to demonstrate an increased overall survival.

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following table contains adverse effects reported mainly in untreated patients.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (7%)	I E
	Arterial thromboembolism (<1%)	I
	Cardiotoxicity (rare)	D
	Hypertension (9%)	I E
	Hypotension (14%)	I
	Venous thromboembolism (rare)	E
Dermatological	Local reactions (>1%)	I
	Rash (12%)	I
Gastrointestinal	Abdominal pain (3%)	E
	Anorexia, weight loss (2%)	E
	Diarrhea (1%)	E
	GI obstruction (rare)	E

	GI perforation (rare)	E
	Mucositis (<1%)	E
	Nausea, vomiting (13%)	I E
General	Fatigue (6%)	E
Hematological	Disseminated intravascular coagulation (rare)	E
	Myelosuppression ± infection, bleeding (63%) (severe)	E
Hepatobiliary	Cholecystitis (rare)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (may be severe)	I
Immune	Autoimmune disorder (rare- hemolytic anemia, ITP, pure red cell aplasia, Goodpastures, Graves, etc.)	E
	Transfusion-associated GVHD	E D
Infection	Immunosuppression/ atypical infection (53%)	E
Metabolic / Endocrine	Tumor lysis syndrome (1%)	I
Musculoskeletal	Musculoskeletal pain (2%)	E
Neoplastic	Secondary malignancy (and leukemia)	D
Nervous System	Anxiety (1%)	E
	Cognitive disturbance (2%)	E
	Dizziness (3%)	I
	Guillain-Barre syndrome	E
	Headache (7%)	I
	Neuropathy	E
	Syncope (1%)	I E
	Tremor (3%)	E
	Vertigo (1%)	E
Ophthalmic	Conjunctivitis (<1%)	E
Renal	Nephrotoxicity (rare)	E
Respiratory	Cough, dyspnea (7%)	I
	Pleural effusion (rare)	E
	Pneumonitis (rare)	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 adverse effects are infusion reactions, myelosuppression, infection, GI and CNS symptoms, fatigue and hypertension. The incidences of these effects are generally lower in previously untreated patients.

Alemtuzumab causes profound **lymphopenia** and results in a variety of **opportunistic infections**, including cytomegalovirus and PCP. Prophylaxis is strongly recommended during treatment and for 2 months after, or until CD4+ counts are >200cells/microL (counts may take up to a year to recover). Blood products administered prior to recovery from lymphopenia should be irradiated because of the potential for **graft versus host disease** in severely lymphopenic patients.

Severe, prolonged, and, in rare instances, fatal, **myelosuppression** has occurred, especially at doses above the recommended doses. If hematologic toxicity is severe, discontinue alemtuzumab. (See Dosing)

Autoimmune diseases, including Graves' disease, hypothyroidism, Guillain-Barre and Goodpasture's syndrome have been reported.

Infusion reactions (IRs) are common, including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, vomiting, and/or rash. Acute infusion-related reactions were most common during the first week of therapy. Antihistamines, acetaminophen, antiemetics, meperidine, and corticosteroids, as well as incremental dose escalation, should be used to prevent or ameliorate infusion-related reactions. IRs with subcutaneous alemtuzumab are much milder (off-label route of administration). Supportive care should be available. Anti-human antibodies are seen in 8% of patients. Patients may cross-react to other monoclonal antibodies.

There have been reports of fatal **progressive multifocal leukoencephalopathy (PML)** in B-CLL patients treated with or without alemtuzumab, Alemtuzumab should be held at first signs or symptoms suggestive of PML and patients suspected of having PML should be investigated appropriately.

There is a risk of serious infusion-related **cardiac complications**, including myocardial infarction and cardiac arrhythmias. Careful monitoring is recommended and resuscitation facilities should be available. Alemtuzumab should only be administered to patients with pre-existing cardiac disease if the benefits outweigh the risks.

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E - Dosing

Refer to protocol by which patient is being treated. Alemtuzumab should be escalated rapidly (usually over 3-7 days) based on tolerance, to the 3 times/week maintenance dose. If therapy is missed for seven or more days, alemtuzumab dose must be re-escalated as below.

Single doses of alemtuzumab greater than 30mg or cumulative weekly doses of greater than 90mg should never be administered.

Adults:

Premedication (prophylaxis for infusion reactions):

Administer 30 minutes prior to IV/SC alemtuzumab*:

- H1-receptor antagonist (e.g. diphenhydramine 50 mg IV)
- Acetaminophen 650 mg PO

*Can consider corticosteroids (methylprednisolone 1g) on the first 3 days

Other supportive care:

- Trimethoprim/sulfamethoxazole DS twice daily three times per week and famciclovir (or equivalent) 250mg bid during treatment and for 2 months after or until CD4+ count is ≥ 200 cells/microL.
- Allopurinol and hydration to reduce the risk of tumour lysis syndrome are recommended.
- Irradiated blood products should be used.

Administration and Escalation

Step		*Dose*	*Next Steps*
1	*Initial dose / restart after ≥ 7days hold*	*3mg Daily as a 2-hour IV infusion*	*When infusion toxicity ≤ G2, then proceed to step #2*
2		*10mg Daily as a 2-hour IV infusion*	*When infusion toxicity ≤ G2, then proceed to step #3*
3	*maintenance*	*30mg 3 x week as a 2-hour IV infusion (Mon-Wed-Fri) for ≤ 12 weeks*	

Dosage with Toxicity:

Dose modification for toxicity:

Toxicity (grade or 10^9)	**1st Occurrence**	**2nd Occurrence**	**3rd Occurrence**
ANC < 0.25 and/or platelet ≤ 25	Hold, restart at same dose when ANC ≥ 0.5 and platelets ≥ 50	Hold, restart at 10mg when ANC ≥ 0.5 and platelets ≥ 50	Discontinue
If baseline ANC ≤ 0.25, and/or platelet ≤ 25 and ↓ 50%	Hold, restart at same dose when ≥ baseline	Hold, restart at 10mg when ≥ baseline	Discontinue
≥ Grade 3 non-hematologic toxicity, including serious infections and CMV viremia	Hold until ≤ grade 2. Consider dose modification		
Autoimmune disorders	Discontinue		
PML, autoimmune anemia or thrombocytopenia	Discontinue		
If delay between dosing is ≥ 7 days, must re-escalate starting from 3mg Do not modify dose for lymphopenia			

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	**Management**	**Re-challenge**
1-2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms resolve, the infusion can be restarted at a slower rate with pre-	• No specific recommendations can be made at this time. If reaction was with IV route, switch to SC if possible.

	medications, unless a serious reaction occurred	
3-4	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Once symptoms resolve, the infusion can be restarted at a slower rate with pre-medications, unless a serious reaction occurred	

Dosage with Hepatic Impairment:

No information found.

Dosage with Renal Impairment:

No information found.

Dosage in the elderly:

Limited experience, no dose modifications appear required.

Children:

The safety and efficacy of alemtuzumab in children have not been studied.

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F - Administration Guidelines

- See the Product Monograph for full details of preparation and administration.
- Full resuscitation facilities and experienced personnel should be available.
- Do not administer as an intravenous push or bolus.
- Mix in 100mL IV bag (5% Dextrose or Normal Saline). Gently invert the bag to mix the solution. Infuse the admixture IV over 2 hours. Other drug substances should not be added or simultaneously infused through the same intravenous line.
- Infusion reactions with subcutaneous alemtuzumab are much milder (off-label route of administration) than IV. Consider subcutaneous administration (except in patients with T-PLL).

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Other:

Alemtuzumab is **contraindicated** in patients with active infections, underlying immunodeficiency (e.g., seropositive for HIV), history of progressive multifocal leukoencephalopathy (PML), known Type I hypersensitivity or anaphylactic reactions to alemtuzumab or any components of MabCampath, or in patients with active secondary malignancies. Gradual escalation to the recommended maintenance dose is required at the initiation of therapy and after interruption of therapy for more than 7 days. Alemtuzumab can result in serious and even fatal infusion reactions. Monitor patients closely during infusions and discontinue alemtuzumab if indicated.

Serious, and in rare instances, fatal pancytopenia, and autoimmune idiopathic thrombocytopenia or hemolytic anemia have occurred. Single doses greater than 30mg or cumulative doses of more than 90mg per week should not be administered, as they are associated with a higher incidence of pancytopenia. Serious and fatal bacterial, fungal, viral, and protozoal infections have been reported. Anti-viral and anti-*Pneumocystis carinii* pneumonia prophylaxis are strongly recommended. All blood products should be irradiated. Live vaccines should not be administered. Use with caution in patients with pre-existing cardiac disease.

It is not known whether alemtuzumab is carcinogenic or mutagenic but is likely to cause fetal harm and to impair fertility. IgG can cross the placental barrier; alemtuzumab should be given to **pregnant** women only if the benefits outweigh the risks to the mother and fetus. Women of childbearing potential and men of reproductive potential should use effective contraceptive methods during

treatment and for a minimum of six months following alemtuzumab therapy. IgG is secreted in human milk; therefore, **breastfeeding** should be discontinued for at least three months after cessation of therapy.

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H - Interactions

No formal drug interaction studies have been performed. An immune response to alemtuzumab may interfere with subsequent diagnostic serum tests that utilize antibodies.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Vaccines	May impair response to vaccinations	Immunosuppression	Avoid
Anticoagulants, NSAIDs, platelet inhibitors, thrombolytic agents	↑ risk of bleeding	Additive	Caution; monitor
Antihypertensives	↑ hypotension	Additive hypotensive effect with infusion reactions	Caution; monitor

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC and platelets	Weekly and as needed
Infusion reactions	During infusion and for at least 2 hours after IV infusion completed
Clinical toxicity assessment for infusion reactions, respiratory and cardiac events, auto-immune disorders, bleeding and infection.	

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Consider CMV monitoring.	
CD4+ counts should be assessed after treatment until recovery to ≥ 200 cells/microL	

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K - References

Product Monograph: MabCampath® (alemtuzumab). Genzyme Canada Inc., March 22, 2010.

Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002;100:768-773.

Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2009;27(24): 3994-4001.

September 2019 Updated infusion reaction information in Adverse Effects, Dosing, Administration and Monitoring sections.

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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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