A DRUG NAME: ALEMTUZUMAB

SYNONYM(S): Campath-1H, human CD52 antibody

COMMON TRADE NAME(S): MabCampath®, Campath ® (Berlex)

B MECHANISMS 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 in non-comparative trials; no data from comparative trials regarding survival or quality of life is available.

Oral Absorption	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 metabolite(s)	No information found
	inactive metabolite(s)	No information found
Excretion	T ½ 11 hours (range: 2-32 hours) after the first 30mg dose and six days (range: 1-14 days) after the last 30mg dose	

C INDICATIONS AND STATUS

* MabCampath is indicated for the treatment of B cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.

Health Canada approved indication

D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT*	ONSET**		
Cardiovascular	Hypotension (30%)	I		
	Hypertension (9%)	I		
	Tachycardia palpitations (5%)	I		
	Chest pain (6%)	I		
	Myocardial infarction (rare)	I		
	Arrhythmia (rare)	I		
	Edema (1%)	I	E	
Nervous System	Headache (18%)	I		
	Paresthesia (6%)		E	
	Tremor (6%)	I	E	
	Dizziness, Vertigo (5%)	I		
	Optic neuritis (rare)		E	
	Depression (2%)			D
	Insomnia (1%)		E	
	Coma, syncope, convulsions (rare)	I	E	
	Guillan Barre (rare)		E	D
	Hyperkinesia (1%)		E	
	Anxiety (3%)		E	
	Somnolence, Confusion (3%)		E	
Extravasation hazard **(refer to Appendix 2)**	Non-vesicant	I		
Dermatologic	Rash, Pruritus (29%)	I		
	Injection site reaction (1%)	I		
Hypersensitivity	Urticaria (28%)	I		
	Bronchospasm (6%)	I		
	Anaphylaxis, angioedema (rare)	I		

D ADVERSE EFFECTS (Continued)

ORGAN SITE	SIDE EFFECT*		ONSET**
Gastrointestinal	Anorexia, Loss of weight (13%)		E
	Dehydration (rare)		E
	Pancreatitis (rare)		E
	Obstruction, perforation (rare)		E
	Nausea , Vomiting (49%)	I	E
	Diarrhea (13%)		E
	Abdominal pain (6%)		E
	Stomatitis/Mucositis all events (10%)		E
	Dyspepsia (4%)		E
	Constipation (2%)		E
	Loss of taste (2%)		E
Musculoskeletal	Myalgia, arthralgia (9%)		E
	Skeletal pain (3%)		E
Pulmonary	Dyspnea, cough (18%) grade 3-4 6%	I	
	Upper respiratory tract infection (6%)		E
	Pneumonia (18%) grade 3-4 13%		E
	Pneumonitis (3%) , ARDS (rare)		E
Renal	Urinary tract infection (3%)		E
	Hematuria (1%)		E
	Renal failure (rare)		E
Generalized	Fever, chills (82%)	I	
	Fatigue (27%)		E
	Pain (7%)		E
	Influenza-like symptoms (5%)	I	
	Conjunctivitis Endopthalmitis (2%)		E

D ADVERSE EFFECTS (Continued)

ORGAN SITE	SIDE EFFECT*	ONSET**
Hematologic	Granulocytopenia (grade 3-4 63%; febrile neutropenia 5%)	E
	Thrombocytopenia (grade 3-4 50%)	E
	Anemia (grade 3-4 38%	E
	Pancytopenia (5%)	E
	Opportunistic infections (10%)	E
	Lymphopenia	E
Metabolic	Hepatic function abnormalities (1%)	E
	Hypocalcaemia, hyponatremia, other electrolyte abnormalities (2%)	E

* Dose-limiting side effects are underlined.
** I = immediate (onset in hours to days) E = early (days to weeks)
D = delayed (weeks to months) L = late (months to years)

Alemtuzumab induced profound **lymphopenia** and a variety of **opportunistic infections** have been reported. Significant numbers of both new and reactivated cytomegalovirus infections have been reported. Anti-infective prophylaxis is strongly recommended at initiation of alemtuzumab therapy and for a minimum of 2 months following completion of therapy, or until CD4+ counts are >200cells/μL.

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 in patients with lymphoma and leukaemia receiving alemtuzumab. Bone marrow **aplasia** and **hypoplasia** have occurred at therapeutic doses; the incidence increases with doses above the recommended dose. Severe and fatal autoimmune **anemia** and **thrombocytopenia** were observed in patients with CLL. If hematologic toxicity is severe, discontinue alemtuzumab.

Autoimmune diseases, including Graves' disease, hypothyroidism, and Goodpasture's syndrome have been reported. Appropriate clinical and laboratory monitoring should be undertaken.

There is a risk of serious infusion related **cardiac complications**, including myocardial infarction, nausea and vomiting, cardiomyopathy, 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 risk.
Infusion reactions are common, including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, 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. Supportive care should be available.

D ADVERSE EFFECTS (Continued)

Patients who develop hypersensitivity to MabCampath may have **allergic** or **hypersensitivity reactions** to other monoclonal antibodies. Second malignancies have been described.

Cases of **Guillain-Barre syndrome** and other **neuropathies** have been reported in association with alemtuzumab treatment.

E DOSING

Refer to protocol by which patient is being treated. Alemtuzumab should be administered under the supervision of a physician experienced in the use of antineoplastic therapy in a setting where full resuscitation facilities are immediately available and personnel are experienced and capable of dealing with severe infusion-related reactions.

Adults:

Premedication: Diphenhydramine 50mg and acetaminophen 650mg administered 30minutes before alemtuzumab infusion should be given prior to the first dose, at dose escalations, and as clinically indicated. Trimethoprim/sulfamethoxazole DS twice daily three times per week and famciclovir (or equivalent) 250mg twice a day upon initiation of alemtuzumab is strongly recommended. Prophylaxis should be continued for two months after completion of alemtuzumab or until CD4+ count is ≥ 200 cells/ μL. Methylprednisolone to ameliorate cytokine release syndrome and allopurinol and hydration to reduce the risk of tumour lysis syndrome is recommended.

Initiation: Alemtuzumab should be initiated at a dose of **3mg** administered as a two-hour IV infusion daily.

Escalation: When the 3mg daily dose is tolerated (infusion-related toxicities are ≤Grade 2), the daily dose should be escalated to **10mg** daily and continued until tolerated.

Maintenance: When the 10mg dose is tolerated, the maintenance dose of **30mg** may be initiated. The maintenance dose is 30mg/day administered three times a week on alternate days (Monday, Wednesday, and Friday) for up to 12 weeks. In most patients escalation to 30mg can be accomplished in 3-7 days.

Dose escalation to the recommended maintenance dose of 30mg three times weekly is required. Single doses of alemtuzumab greater than 30mg or cumulative weekly doses of greater than 90mg should not be administered since higher doses are associated with an increased incidence of pancytopenia.

If therapy is missed for seven or more days, alemtuzumab should be reinstated with gradual dose escalation.

E DOSING (Continued)

Dose modification for hematologic toxicity:

Hematologic Toxicity (cells/mm^3)	Dose modification and Reinitiating Therapy
1st occurrence of ANC<250/ µL and/or platelet count ≤ 25,000/ µL	Hold alemtuzumab. Resume when ANC≥ 500/ µL, platelet ≥ 50,000/ µL at the same dose. If ≥7 days delay reduce to 3mg, escalate to 10mg and then 30mg as tolerated.
2nd occurrence of ANC<250/ µL and/or platelet count ≤ 25,000/ µL	Hold alemtuzumab. Resume when ANC≥ 500/ µL. platelets ≥ 50,000/ µL, at **10mg**. If ≥7 days delay reduce to 3mg, escalate to 10mg.
3rd occurrence of ANC<250/ µL and/or platelet count ≤ 25,000/ µL	Permanently discontinue alemtuzumab therapy.
For patients with marrow impairment at baseline (ANC ≤ 500/µL and/or platelets ≤ 25,000/ µL) whose ANC and/or platelet count fall to ≤ 50% of the baseline	Hold alemtuzumab therapy. Resume when AND and/or platelets return to baseline value(s). If ≥7 days delay reduce to 3mg, escalate to 10mg..

Dosage with serious infection: Hold until resolved then restart cautiously.

Dosage in renal impairment: No information found.

Dosage in hepatic impairment: No information found.

Dosage in the elderly: Based on available PK data, no dose modifications are required.

***Children*:** The safety and effectiveness of alemtuzumab in children has not been studied.

F ADMINISTRATION GUIDELINES (see Appendix 3a)

- Alemtuzumab should be administered under the supervision of a physician experienced in the use of antineoplastic therapy in a setting where full resuscitation facilities are immediately available and personnel are experienced and capable of dealing with severe infusion-related reactions.
- **Do not administer as an intravenous push or bolus.**
- Filter Alemtuzumab with a sterile, low-protein binding, non-fiber releasing 5 µm filter prior to dilution. Mix in 100mL IV bag (5% Dextrose or Normal Saline). Gently invert the bag to mix the solution. Infuse the admixture over 2 hours.
- Although not approved by Health Canada, Alemtuzumab has been given subcutaneously instead of intravenously ; the incidence of infusion reactions may be lower.
- Other drug substances should not be added or simultaneously infused through the same intravenous line. While not classified as a vesicant or irritant, precautions should be taken to avoid extravasation. A free-flowing intravenous line should be established prior to administration of alemtuzumab. Close monitoring for evidence of extravasation is required. If any signs or symptoms of extravasation occur, the infusion should be immediately terminated and restarted in another vein.
- See the Product Monograph for full details of preparation and administration.

G SPECIAL PRECAUTIONS

Alemtuzumab is contraindicated in patients with active infections, underlying immunodeficiency (e.g., seropositive for HIV), 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 is 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. 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 crosses the placenta, therefore breast-feeding should be discontinued for at least three months after cessation of therapy.

H INTERACTIONS*

AGENT	EFFECT	MECHANISM	MANAGEMENT
Vaccines	May impair response to vaccinations	Immunosuppression	Avoid
Anticoagulants	May increase bleeding	Additive effect	Monitor
Antiplatelet agents	May increase bleeding	Additive effect	Monitor
Antihypertensives	Hypotension	Additive hypotensive effect with infusion reactions	Monitor

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

I RECOMMENDED CLINICAL MONITORING

Recommended Clinical Monitoring	**Suggested Clinical Monitoring**
• Complete blood count (CBC) and platelets should be checked weekly and more frequently if worsening anemia, neutropenia, or thrombocytopenia is observed. • CD4+ counts should be assessed after treatment until recovery to >/= 200cells/µL • Monitor vital signs, including blood pressure and signs of hypotensive symptoms, and signs and symptoms of infusion-related or allergic reactions during each of the infusions. • Monitor all patients closely, especially those with pre-existing cardiac and pulmonary conditions or prior significant cardiac adverse events.	• Investigate and monitor for auto-immune disorders

J REFERENCES

E-CPS, MabCampath® monograph, accessed 15 July 2006

Campath® monograph, Genzyme and Berlex (United States), 1 July 2006

E-Drugdex® Evaluations, Alemtuzumab monograph, accessed 1 July 2006

Alemtuzumab: ADIS drug profile, Drugs 2003: 63 (12): 1229-1243

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, Winkler D, Krober A, et al. Subcutaneous campath-1H (alemtuzumab) in fludarabine-refractory CLL: interim analysis of the CLL2h study of the German CLL Study Group (GCLLSG). [abstract]. Blood. 2004;104(11): A487.