DRUG NAME: Blinatumomab

SYNONYM(S): MT-103[1], AMG-103[1], MEDI-538[1]

COMMON TRADE NAME(S): BLINCYTO®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Blinatumomab is a bispecific monoclonal antibody that binds to CD3 on T cells and CD19 on B cells. By forcing B and T cells into close proximity, blinatumomab causes the formation of cytolytic synapses between B and T cells. T cells release perforin and granzymes through synapses into B cells which results in apotosis and lysis of normal and malignant CD19 positive B cells. Blinatumomab is associated with transient up-regulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells. Blinatumomab is an immunosuppressive agent.[2]

PHARMACOKINETICS:

Absorption	following continuous intravenous infusion, steady state concentration (Css) achieved within 1 day	
Distribution	linear pharmacokinetics; mainly distributed into the vascular space	
	cross blood brain barrier?	no information found
	volume of distribution	4.52 L
	plasma protein binding	no information found
Metabolism	possibly degrades catabolically into small peptides and amino acids	
	active metabolite(s)	unknown
	inactive metabolite(s)	unknown
Excretion	rapid elimination; requires continuous IV infusion to maintain therapeutic concentrations	
	urine	negligible amounts
	feces	no information found
	terminal half life	2.11 hours
	clearance	2.92 L/hour
Children[3]	comparable to adults over a dose range of 5-30 mcg/m^2/day	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Leukemia, acute lymphoblastic

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- ***hospitalization*** is recommended for the first nine days of cycle 1 and the first two days of cycle 2; supervision or hospitalization may be considered for subsequent cycles and treatment interruptions lasting longer than 4 hours[2]
- ***dexamethasone premedication*** is recommended prior to each cycle to prevent infusion reactions[2]
- ***cytokine release*** and ***tumour lysis syndrome*** have occurred in patients with a high tumour burden[3]
- ***live vaccines*** are not recommended during treatment; if required, vaccination should be completed either 2 weeks prior to the first treatment or after B cell recovery post-treatment [2]
- ***pancreatitis*** has been reported; high dose steroids may be contributory[3]

Special populations:
- patients 65 years of age or greater are at an increased risk of serious infections, as well as serious neurologic events including encephalopathy, confusion, and cognitive disorder[2]
- pediatric patients experience increased rates of anemia, thrombocytopenia, vomiting, pyrexia, and hypertension[4]
- in patients less than two years of age, neurologic toxicities may present as agitation, headache, insomnia, somnolence, and irritability[4]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animals, there were no effects on reproductive organ weights or histopathology.[2,5]

Pregnancy: In animal studies, no embryotoxicity or teratogenicity was observed. However, due to potential for lymphocytopenia and increased infection risk in infants born to mothers exposed to blinatumomab, women of childbearing potential should use contraception during, and for at least 48 hours after the last dose of blinatumomab. In addition, due to the potential depletion of B cells in newborns exposed to blinatumomab during pregnancy, B cell counts should be monitored and vaccinations with live virus vaccines should be postponed until the infant's B cell counts return to normal.[2]

Breastfeeding is not recommended during and for at least 48 hours after treatment due to the potential secretion into breast milk.[2]

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.[6-9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (18-20%, severe 13-14%)[2,10]
	febrile neutropenia (25-28%, severe 23-25%)[2,10]
	leukocytosis (3%)
	leukopenia (10%, severe 8%)
	lymphopenia (severe 38%)
	neutropenia (severe 19%)
	thrombocytopenia (11%, severe 9%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	sinus tachycardia (6%)
	tachycardia (6%)
eye	blurred vision (6%)
gastrointestinal	*emetogenic potential:* low[11]
	abdominal distension (6%, severe 1%)
	abdominal pain (17%, severe 3%)
	constipation (21%, severe 1%)
	diarrhea (18%, severe 1%)
	nausea (24%)
	pancreatitis (<1%); has been fatal, may require treatment interruption or discontinuation
	vomiting (13%)
general disorders and administration site conditions	*extravasation hazard:* none[12]
	asthenia (10%, severe 3%)
	chest pain (11%, severe 1%)
	chills (15%)
	edema (6%, severe 1%)
	fatigue (15-17%, severe 1%)[2,10]
	pain (7%, severe 1%)
	peripheral edema (26%, severe 1%)
	pyrexia (60%, severe 7%)
immune system (see paragraph following **Side Effects** table)	***cytokine release syndrome*** (11-12%, severe 1%)[2,10]
	hypersensitivity (2%)
	infusion reaction (29%)
infections and infestations (see paragraph following **Side Effects** table)	bacterial infection (21%, severe 13%)
	fungal infection (14%, severe 7%)
	infection, unspecified pathogen (43%, severe 25%)
	pneumonia (10%, severe 9%)
	sepsis (7%, severe 6%)
	upper respiratory tract infection (5%)
	viral infection (12%, severe 5%)
investigations (see paragraph following **Side Effects** table)	***ALT increase*** (13%, severe 7%)
	AST increase (11%, severe 6%)
	bilirubin increase (8%, severe 4%)
	gamma-glutamyltransferase increase (5%, severe 4%)
	weight gain (9%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
metabolism and nutrition	appetite decrease (10%, severe 3%)
	hyperglycemia (13%, severe 8%)
	hypoalbuminemia (5%)
	hypocalcemia (severe 5%)
	hypokalemia (24%, severe 7%)
	hypomagnesemia (13%)
	hypophosphatemia (7%, severe 5%)
	tumour lysis syndrome (4%); see paragraph following **Side Effects** table
musculoskeletal and connective tissue	arthralgia (11%, severe 2%)
	back pain (14%, severe 2%)
	bone pain (10%, severe 3%)
	muscle spasms (5%)
	muscle weakness (8%, severe 2%); see paragraph following **Side Effects** table
	myalgia (9%, severe 1%)
	pain in extremity (11%, severe 1%)
nervous system (see paragraph following **Side Effects** table)	aphasia (4%)
	ataxia (5%)
	cognitive disorder (2%)
	convulsion (2%)
	dysarthria (3%)
	dizziness (14%, severe 1%)
	encephalopathy (5%, severe 3%); see paragraph following **Side Effects** table
	headache (34-36%, severe 3-4%)[2,10]
	lethargy (3%)
	leukoencephalopathy (<1%); reported in patients with prior cranial irradiation and chemotherapy such as high dose methotrexate or intrathecal cytarabine
	memory impairment (2%)
	paresthesia (4%)
	peripheral neuropathy (3%)
	somnolence (5%)
	tremor (18%, severe 1%)
psychiatric	anxiety (7%)
	confusion (7%, severe 2%); see paragraph following **Side Effects** table
	insomnia (15%)
respiratory, thoracic and mediastinal	cough (19%)
	dyspnea (9-15%, severe 3-5%)[2,10]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	epistaxis (6%)
skin and subcutaneous tissue	rash (12-21%, severe 2-3%)[2,10]
	petechiae (6%, severe 1%)
vascular	capillary leak syndrome (<1%)
	hypertension (6%, severe 4%)
	hypotension (12%, severe 3%)

Adapted from standard reference[2] unless specified otherwise.

Cytokine release syndrome (CRS), including cytokine storm, occurs early in treatment and may be severe or life-threatening. Patients with elevated LDH or a high tumour burden (i.e., ≥ 50% leukemic blasts in bone marrow or > 15 x 10^9/L peripheral blood leukemic blast counts) are at a greater risk of developing CRS. Symptoms include pyrexia, headache, nausea, asthenia, hypotension, and increased transaminases or total bilirubin. CRS has also been associated with disseminated intravascular coagulation, capillary leak syndrome, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Cytokine elevation peaks within the first 2 days of therapy with blinatumomab, therefore risk of reaction is mitigated by initiating cycle 1 treatment with a lower starting dose for one week prior to escalation to full treatment dose. Based on tumour burden, consider pretreating with dexamethasone for up to four days prior to initiating blinatumomab therapy. Management of CRS may require temporary interruption or discontinuation of blinatumomab.[1,10,13,14]

Infusion-related reactions may be clinically indistinguishable from cytokine release syndrome. Premedicate with dexamethasone prior to each cycle, and as clinically indicated. Observe closely for reactions, especially during the first infusions of both the first and second cycles as well as with dose escalation. Interrupt or discontinue blinatumomab based on the severity of the reaction.[2,14]

Hyperuricemia may result from ***tumour lysis*** caused by blinatumomab and may lead to electrolyte disturbances or acute renal failure.[15] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[16]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[17] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[18]

Transient ***liver enzyme elevations*** may occur independently of cytokine release syndrome. The majority of these events are reported within the first one to two weeks of treatment and do not require treatment modification. Treatment interruption is recommended if AST/ALT rises to greater than 5 times the upper limit of normal or if total bilirubin rises to more than 3 times the upper limit of normal.[2,10,14]

Neurologic events occur in approximately half of adult patients, with a median time to onset of nine days. They are predominately mild to moderate in severity, although life-threatening and fatal events have also been reported. Severe (i.e., grade 3 or greater) neurologic events include encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion, disorientation, and coordination and balance disorders. Manage severe

events by interrupting treatment for at least three days and until neurologic symptoms improve to grade 1. Premedicate with intravenous dexamethasone. As secondary prophylaxis, consider appropriate anticonvulsants prior to reinitiating blinatumomab at the starting dose. Permanent discontinuation of blinatumomab should be considered following:

- any life-threatening neurologic event,
- occurrence of more than one seizure,
- neurologic events which require greater than one week to improve to grade 1 with treatment interruption, or
- a severe neurologic event requiring treatment interruption that occurs at the lowest starting dose.

Advise patients to use caution or to avoid driving and operating heavy machinery during treatment because of the risk of loss of consciousness and seizures secondary to treatment.[2,10,13]

Serious bacterial and fungal infections have been reported in approximately 25% of patients receiving blinatumomab and are sometimes fatal. Consider prophylactic antibiotics for at-risk patients. Treat infection and interrupt or discontinue blinatumomab as indicated.[2]

INTERACTIONS: no information found

SUPPLY AND STORAGE:

Injection**:** Amgen Canada Inc. supplies blinatumomab as 38.5 mcg single-use (preservative free) vials of sterile lyophilized powder. Each package contains a preservative-free IV solution stabilizer which is supplied in 10 mL single-use vials. Refrigerate. Protect from light. [2]

Additional information[2]: Intact vials of drug and IV solution stabilizer are stable at room temperature for 8 hours.

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information[2]:

- Preparation
  - IV solution stabilizer is used to coat the prefilled IV bag before adding reconstituted blinatumomab; do NOT use the IV solution stabilizer to reconstitute blinatumomab
  - use only non-DEHP bags and administration sets
- Administration
  - prime IV tubing with prepared infusion solution; do NOT prime with normal saline
  - administer using a low protein-binding 0.2 or 0.22 micron in-line filter
  - the total volume of the compounded infusion bag will exceed the administered volume; ONLY 240 mL of the prepared bag should be administered
  - do NOT flush IV lines at infusion completion or when changing infusion bags; this may cause the inadvertent administration of a drug bolus to the patient

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	no information found
Continuous infusion[2]	***over 4 weeks;*** use non-DEHP bags and administration sets
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*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***6 weeks***:	Patients ≥ 45 kg (fixed dose)[3,19] Cycle 1: ***9 mcg/day*** by ***continuous IV infusion*** on ***days 1-7***, followed by ***28 mcg/day*** on ***days 8-28*** (total dose for cycle 1 = 651 mcg) Cycles 2-5: ***28 mcg/day*** by ***continuous IV infusion*** on ***days 1-28*** (total dose per cycle = 784 mcg) Patients < 45 kg (BSA based dose)[3] Cycle 1: 5 mcg/m^2/day (max 9 mcg/day) by continuous IV infusion on days 1-7, followed by 15 mcg/m^2/day (max 28 mcg/day) on days 8-28 (total dose for cycle 1 = 350 mcg/m^2) Cycle 2-5: 15 mcg/m^2/day (max 28 mcg/day) by continuous IV infusion on days 1-28 (total dose per cycle = 420 mcg/m^2)
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated	

BCCA usual dose noted in ***bold, italics***

Cycle Length:

Dosage in renal failure[10]

Creatinine clearance (mL/min)	Dose
>30	100%
<30	no information found

calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L

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

Dosage in hepatic failure: no information found

Dosage in dialysis: no information found

Children:

Cycle Length:

Intravenous:

6 weeks:

Patients ≥ 45 kg (fixed dose)[3,4]
Cycle 1:
9 mcg/day by continuous IV infusion on days 1-7, followed by 28 mcg/day on days 8-28

Cycles 2-5:
28 mcg/day by continuous IV infusion on days 1-28

Patients < 45 kg (BSA based dose)[3,4]
Cycle 1:
5 mcg/m^2/day (max 9 mcg/day) by continuous IV infusion on days 1-7,
followed by 15 mcg/m^2/day (max 28 mcg/day) on days 8-28

Cycle 2-5:
15 mcg/m^2/day (max 28 mcg/day) by continuous IV infusion on days 1-28

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