DRUG NAME: Bendamustine

SYNONYM(S):

COMMON TRADE NAME(S): TREANDA®

CLASSIFICATION: Alkylating agent

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

MECHANISM OF ACTION:

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Its exact mechanism of action is unknown, but it may cause apoptotic and non-apoptotic death of malignant cells by damaging both single- and double-strand DNA, increasing the expression of pro-apoptotic genes, and inhibiting mitotic control. Bendamustine is active against both quiescent and dividing cells.[1]

PHARMACOKINETICS:

Distribution	not extensively distributed in tissues	
	cross blood brain barrier?	no information found
	volume of distribution	20-40 L
	plasma protein binding	94-96% *(in vitro)*; however not considered likely to displace or be displaced by highly protein-bound drugs
Metabolism	primarily via hydrolysis; also via oxidative and conjugative pathways	
	active metabolite(s)	gamma-hydroxy bendamustine and N-desmethyl-bendamustine (via CYP 1A2); cytotoxic activity primarily from parent compound[2]
	inactive metabolite(s)	monohydroxy and dihydroxy-bendamustine (via hydrolysis)
Excretion	rapid elimination of bendamustine and active metabolites	
	urine	3% (as parent compound); <1% (as active metabolites); <5% (as inactive metabolites)
	feces	90%[3]
	terminal half life	40 min (parent compound); 3.7 h (active metabolites)
	clearance	32-42 L/h
Sex	no significant differences	
Elderly	no significant differences	
Ethnicity	limited data; effect of race has not been established	

Adapted from standard reference[4,5] unless specified otherwise.

USES:

Primary uses:
*Lymphoma, non-Hodgkin's
*Leukemia, chronic lymphocytic

Other uses:
Lymphoma, Hodgkin's[6]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications: history of hypersensitivity reaction to bendamustine or mechlorethamine.

Caution:

- ***infusion reactions*****,** including fever, chills, pruritus, and rash commonly occur[1]
- ***tumour lysis syndrome*** has been associated with bendamustine with usual onset occurring during the first cycle; the use of allopurinol concurrently with bendamustine may increase the risk of severe skin toxicity[1]
- ***myelosuppression*** is likely with bendamustine; hematologic nadirs predominantly occur in third week of therapy[4]
- avoid bendamustine in patients with ***serious infections***, including HIV; infections have been associated with hospitalization, septic shock, and death[4]
- avoid ***live attenuated vaccines*** during treatment with bendamustine[4]
- ***hypertension***, including hypertensive crisis, has been reported with bendamustine; hypertension should be well-controlled prior to treatment with bendamustine[4]

Carcinogenicity: Pre-malignant and malignant diseases (i.e., myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma) have been reported with bendamustine. Bendamustine has also been shown to be carcinogenic in mice.[4]

Mutagenicity: Mutagenic in *in vitro* bacterial reverse mutation assay. Bendamustine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[4]

Pregnancy: FDA Pregnancy Category D.[1] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Bendamustine is embryotoxic and teratogenic in toxicology studies in mice and rats. There are no studies in pregnant women. Effective contraception is recommended, starting 2 weeks prior to treatment and continuing until at least 4 weeks post-treatment, for men and women of childbearing potential.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk.

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]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia (see paragraph following **Side Effects** table)	***anemia*** (19-94%, severe 2-13%)
	febrile neutropenia (6%, severe 6%)
	leukopenia (16-94%, severe 12-56%)
	lymphopenia (6-99%, severe 6-94%)
	neutropenia (27-86%, severe 23-61%)
	thrombocytopenia (23-88%, severe 12-25%)
cardiac (see paragraph following **Side Effects** table)	cardiorespiratory arrest (2%)
	chest pain (6%)
	myocardial infarction (≤3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	tachycardia (2-7%)
gastrointestinal	*emetogenic potential:* low-moderate[8]
	abdominal pain (5-14%, severe 1%)
	anorexia, decreased appetite (12-24%, severe 1-3%)
	constipation (15-31%, severe <1%)
	dehydration (14-15%, severe 5-6%)
	diarrhea (9-42%, severe 1-5%)
	dry mouth (9%)
	dysgeusia (11%)
	dyspepsia (11-16%, severe 2%)
	gastrointestinal reflux disease (11%)
	nausea (19-77%, severe <4%)
	pharyngolaryngeal pain (8-10%, severe ≤1%)
	stomatitis (15-21%, severe <1%)
	vomiting (16-40%, severe <2%)
general disorders and administration site conditions	*extravasation hazard:* irritant[9,10]
	catheter/ infusion site pain (5-7%)
	chills (6-14%)
	fatigue (9-64%, severe 1-14%)
	injection site reactions, including erythema, phlebitis, pruritus, marked swelling, and pain (2-7%)
	night sweats (5%)
	pyrexia (24-36%, severe 1-4%)
hepatobiliary	hepatotoxicity (2%)
immune system	***hypersensitivity*** (5%, severe 1%)
	infusion reactions, anaphylaxis; see paragraph following **Side Effects** table
infections and infestations	cytomegalovirus infection (3-5%, severe 3%)
	herpes simplex (3-6%)
	herpes zoster (10-12%, severe 3-4%)
	nasopharyngitis (6-9%)
	oral candidiasis (6%, severe 1%)
	pneumonia (8-9%, severe 5%)
	sepsis (1-2%)
	sinusitis (8-9%)
	upper respiratory tract infection (9-10%)
	urinary tract infection (10-11%, severe 2-3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
investigations	albumin elevation (2%)
	ALT elevation (3%)
	AST elevation (1%)
	hyperbilirubinemia (2-3%)
	serum creatinine elevation (5%, severe 1-3%)
	weight loss (6-30%, severe 2-3%)
metabolism and nutrition	dehydration (severe 5%)
	hyperglycemia (5%)
	hyperkalemia (<1%)
	hyperuricemia (7%, severe 2%)
	hypocalcemia (3%)
	hypoglycemia (3%)
	hypokalemia (2-11%, severe 5-6%)
	hypomagnesemia (5%, severe 2%)
	hyponatremia (3%, severe 2%)
	tumour lysis syndrome (1-2%); see paragraph following **Side Effects** table
musculoskeletal and connective tissue	arthralgia (6%)
	asthenia (8-13%, severe 2-4%)
	back pain (13-14%, severe 3%)
	bone pain (5%)
	myalgia (5%)
	pain in extremity (5-6%, severe 1-2%)
	pain, unspecified (6-9%)
neoplasms	pre-malignant and malignant diseases (including myelodysplastic syndrome, anaplastic large T-cell lymphoma, squamous cell carcinoma, myeloproliferative disorders, acute myeloid leukemia, bronchial carcinoma)
nervous system	dizziness (14-15%)
	headache (21%)
	insomnia (13-15%)
psychiatric	anxiety (8%)
	depression (5-6%)
renal and urinary	acute renal failure (1%)
respiratory, thoracic and mediastinal	***cough*** (4-22%, severe ≤1%)
	dyspnea (2-17%, severe 2%)
	nasal congestion (5%)
	respiratory failure (<2%)
	wheezing (5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
skin and subcutaneous tissue (see paragraph following **Side Effects** table)	dry skin (5-7%)
	hyperhidrosis (5%)
	pruritus (5-6%)
	rash (8-28%, severe 1-3%); may be progressive and increase in severity, may require treatment cessation
	Stevens-Johnson syndrome (<1%)
	toxic epidermal necrolysis (<1%)
vascular	edema, peripheral (13-14%, severe <1%)
	hypertension (3%, severe 3-5%)
	hypertensive crisis (2%)
	hypotension (6-8%, severe 1-2%)

Adapted from standard reference[1,4] unless specified otherwise.

Cardiac failure, myocardial infarctions, palpitations, angina pectoris, arrhythmias, pericardial effusion, and tachycardia have been reported. Periodic monitoring of ECG is suggested in patients with cardiac disorders, particularly in the presence of electrolyte imbalances.[4]

Infusion reactions generally develop during or directly after drug administration. Symptoms include fever, chills, pruritus, shortness of breath, hypotension, cyanosis, tachycardia, and rash. Rarely, severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. In patients experiencing grade 1 or 2 infusion reactions, consider premedicating with antihistamines, antipyretics, and corticosteroids to prevent reactions in subsequent cycles. Discontinue bendamustine for severe reactions.[4,11] Refer to BC Cancer Protocol SCDRUGRX:Management of Hypersensitivity Reactions to Chemotherapeutic Agents.

Myelosuppression is likely with bendamustine; common hematologic events include neutropenia, thrombocytopenia, anemia, and leucopenia. Hematologic nadirs are observed predominantly in the third week of therapy. Myelosuppression is reversible, although dose reduction or delay may be required.[4,11] Colony-stimulating factors and blood product replacement have been used to manage myelosuppression.[11]

A number of ***skin reactions***, including rash, toxic skin reactions, and bullous exanthema have been reported. Skin reactions may be progressive and increase in severity with further treatment with bendamustine. Withhold or discontinue bendamustine for severe or progressive skin reactions. There may be an increased risk of severe skin toxicity when bendamustine is administered concomitantly with allopurinol; cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, some fatal, have been reported when bendamustine was administered with allopurinol.[4]

Tumour lysis syndrome has been associated with bendamustine, and may lead to acute renal failure, cardiac arrhythmias, or death. Usual onset occurs during the first cycle. Maintenance of adequate volume status and monitoring of blood chemistry, including potassium and uric acid levels is suggested. Allopurinol has been used in the management of tumour lysis syndrome; however, the concomitant use of bendamustine and allopurinol may increase the risk of severe skin toxicity.[1]

INTERACTIONS:

Bendamustine's active metabolites, gamma-hydroxy bendamustine and N-desmethyl-bendamustine are formed via CYP 1A2; therefore, inhibitors and inducers of CYP 1A2 may affect the circulating levels of bendamustine and its active metabolites. Clinical significance is unknown.[4]

Bendamustine is considered unlikely to inhibit or induce the metabolism of substrates of CYP isoenzymes.[4]

In vitro data suggest that bendamustine may be a substrate for P-glycoprotein. Clinical significance is unknown.[4]

SUPPLY AND STORAGE:

Injection: Teva Canada Limited supplies bendamustine as 25 mg and 100 mg single-use vials of lyophilized powder. Store at 2-25°C. Protect from light.[12]

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	no information found
Intermittent infusion[12-17]	***over*** 30-***60 minutes***
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***

Intravenous:

Cycle Length:

4 weeks[12-17]: ***70-90 mg/m²*** (range 70-100 mg/m²) ***IV for one dose on days 1 and 2***
(total dose per cycle range 140-200 mg/m²)

3 weeks[12]: 120 mg/m² IV for one dose on days 1 and 2
(total dose per cycle 240 mg/m²)

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated.
Dose re-escalation may be considered in subsequent cycles.[4]

Dosage in renal failure:

- mild or moderate impairment does not appear to affect systemic exposure to bendamustine[3,5];
- has been used without dose reduction in renal failure and end-stage renal disease[18-21]

Dosage in hepatic failure: mild impairment does not appear to affect systemic exposure to bendamustine[3,5]; avoid use with AST/ALT ≥ 2.5 x ULN or bilirubin ≥ 1.5 x ULN[2,11]

Dosage in dialysis: physicochemical characteristics of drug suggest that significant drug removal is unlikely during dialysis[22]; has been used without dose reduction in dialyzed patients[19,20]

Children: no information found

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