

Drug Monograph

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A - Drug Name

bendamustine

SYNONYM(S): cytotasan hydrochloride, SDX-105

COMMON TRADE NAME(S): Treanda®

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B - Mechanism of Action and Pharmacokinetics

Bendamustine is a mechlorethamine derivative containing a purine-like benzimidazole ring and is an alkylating agent. It shows limited cross resistance to other alkylating agents.

The efficacy of bendamustine in patients with relapsed indolent B-cell NHL is based on overall response rate and duration of response data from a single-arm pivotal trial (SDX-105-03).

The efficacy in treatment-naïve patients with symptomatic CLL is based on progression-free survival and overall response rate of bendamustine compared to chlorambucil.

Absorption	Dose proportionality of bendamustine has not been studied in humans but plasma concentrations were often greater than dose proportional in animal studies.	
Distribution	PPB	94 - 96%
	Cross blood brain barrier?	Not significant
	Distribution Sites	kidneys and liver (mice and rat models)
Metabolism	Extensively metabolized via hydrolytic and conjugative pathways. Oxidative metabolism also occurs via CYP1A2 to form active minor metabolites.	

	Main enzymes involved	CYP1A2
	Active metabolites	M3 and M4 (minor)
	Inactive metabolites	monohydroxy and dihydroxy-bendamustine metabolites (major)
Elimination	Urine	46% (minor pathway for unmodified bendamustine)
	Feces	25%
	Clearance	700 mL/minute
	Half-life	40 minutes

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C - Indications and Status

Health Canada Approvals:

- Relapsed indolent B-cell non-Hodgkin Lymphoma (NHL) patients who did not respond to or progressed during or shortly following treatment with a rituximab regimen.
- Symptomatic chronic lymphocytic leukemia (CLL) patients who have received no prior treatment.

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D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Irritant

(from NHL trials in general)

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (5%)	E

	Arterial thromboembolism (rare)	E
	Cardiotoxicity (rare)	E D
	Hypertension (5%) (may be severe)	I E
	QT interval prolonged (rare)	E
	Sudden death (2%)	E D
Dermatological	Rash, pruritus (15%) (may be severe)	E D
Gastrointestinal	Abdominal pain (14%)	E
	Anorexia, weight loss (24%)	E D
	Constipation (31%)	E
	Diarrhea (42%)	E
	Dyspepsia (14%)	E
	Mucositis (21%)	E
	Nausea, vomiting (77%)	I E
General	Fatigue (64%)	I E
	Fever, chills (36%)	E
	Fluid retention (14%)	E D
	Pain (9%)	E
Hematological	Myelosuppression ± infection, bleeding (4%) (Grade 3 or 4; may be severe)	E
Hepatobiliary	↑ LFTs (3%) (Grade 3 or 4; may be severe)	E
Hypersensitivity	Infusion related reaction (5%)	I
Infection	Immunosuppression/ atypical infection (12%)	E D
Injection site	Pain (7%)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (11%)	E D
	Tumor lysis syndrome (2%)	E
Musculoskeletal	Pain (13%)	E
Neoplastic	Secondary malignancy (1%) (includes MDS, lymphoma and squamous cell carcinoma)	D L
Nervous System	Dizziness (15%)	I E
	Dysgeusia (11%)	E
	Headache (21%)	E
	Insomnia (15%)	E
	Mood changes (8%)	E D
Renal	Renal failure (1%)	D

Respiratory	Acute respiratory distress syndrome (ARDS) (rare)	E
	Cough, dyspnea (17%)	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 side effects for bendamustine include nausea, vomiting, fatigue, myelosuppression, diarrhea, fever, chills, constipation, anorexia, weight loss, headache and mucositis.

Secondary malignancies (mainly hematologic) have been reported with bendamustine use.

Cardiac disorders (may be severe and fatal) have been reported in patients receiving bendamustine. Correct for hypokalemia and other electrolyte abnormalities prior to and during treatment with bendamustine, especially in patients with pre-existing cardiac disorders.

Hypertension, including hypertensive crisis, have been reported. Blood pressure should be well-controlled prior to starting treatment with bendamustine.

Tumour lysis syndrome, particularly with bulky disease, may occur within the first treatment cycle. Preventative measures, including adequate volume status and correction of electrolytes (particularly potassium and uric acid), is recommended. If using allopurinol concurrently with bendamustine, an increased risk of severe **skin toxicity** (including Stevens-Johnson syndrome and toxic epidermal necrolysis) was noted.

Myelosuppression occurred commonly and was fatal in 2% of patients in the NHL study. Infections, including atypical infections such as CMV and HZV are common. Reactivation of hepatitis B in patients who are chronic carriers has occurred and may be fatal. Patients should be monitored for atypical infections and receive appropriate prophylaxis and/or treatment as required.

Infusion reactions are common. Symptoms were generally mild but severe anaphylactic and anaphylactoid reactions were described, particularly in the second and subsequent cycles of treatment. Patients who experience Grade 3 or worse allergic-type reactions should not be rechallenged. Preventative measures to prevent Grade 1 or 2 reactions on subsequent cycles include antihistamines, antipyretics and corticosteroids should be considered.

Bendamustine **extravasation** has resulted in hospitalizations. Injection sites should be monitored for redness, swelling, pain, infection and necrosis during and after administration.

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist depending on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Do not retreat until ANC $\geq 1 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$ and non-hematologic toxicity has recovered to \leq grade 1.

Adults:

Pre-medication (only for patients with Grade 1 or 2 reactions with prior infusion):

- Analgesic/antipyretic (e.g. acetaminophen), corticosteroid and an antihistamine (e.g. diphenhydramine) should be considered in subsequent cycles.

Dosing instructions

Setting	Dosing	Dose level -1	Dose level -2
Non-Hodgkin's Lymphoma*	120 mg/m ² on Days 1 and 2 of a 21-day cycle; up to 8 cycles	90 mg/m ²	60 mg/m ²
Chronic Lymphocytic Leukemia**	100 mg/m ² on Days 1 and 2 of a 28-day cycle; up to 6 cycles	50 mg/m ²	25 mg/m ²

*Do not re-escalate after dose modification for toxicity

**Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician

Dosage with Toxicity:

Toxicity	Modification
Grade 4 Hematologic toxicities	Delay until ANC $\geq 1 \times 10^9/L$, platelets $\geq 75 \times 10^9/L$ then reduce by 1 dose level
\geq Grade 3 Hypersensitivity reaction	Discontinue
\geq Grade 2 clinically significant Non-hematologic toxicities;	Delay until recovered to \leq grade 1, then reduce by one dose level

≥ Grade 3 Non-hematologic toxicities	
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Dosage with Hepatic Impairment:

Bilirubin	AST or ALT or ALP	Dose
< 1.5 x ULN	2.5 x ULN	Caution
> 1.5 x ULN	> 2.5 x ULN	Do not use

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Dose
>80	100%
40 - 80	Caution
< 40	Do not use

Dosage in the elderly:

No dose adjustment required. No clinically significant differences in efficacy and safety were observed in those aged 65 and older and younger patients.

Children:

Safety in children has not been established. A phase II study did not support efficacy in pediatric patients.

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F - Administration Guidelines

- **NHL** - infuse over 60 minutes
- **CLL** - infuse over 30 minutes

- Bendamustine infusions should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions.
- **DO NOT** administer as an IV push or bolus.
- **Dilute** to a final concentration of 0.2 - 0.6 mg/mL in 500 mL infusion bag of 0.9% sodium chloride or 2.5% dextrose/0.45% sodium chloride.
- Reconstituted solution must be transferred to infusion bag within 30 minutes of reconstitution.
- Administer bendamustine through a dedicated line.
- Compatible with PVC or polyethylene bags.
- Do not admix with other drugs.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components (including mannitol)
- Patients with CrCl < 40 mL/min or moderate/severe hepatic impairment
- Patients with serious infections

Other Warnings/Precautions:

- Avoid live or live-attenuated vaccines, since they may result in serious or fatal infections in patients immunocompromised by bendamustine
- Avoid in patients with relapsed indolent NHL who did not tolerate prior therapies (including other alkylating agents)
- Use with caution in patients with hypertension and patients with mild renal and hepatic impairment

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Documented in animals
- Genotoxicity: Documented in animals
- Embryotoxicity: Documented in animals
- Teratogenicity: Documented in animals
- Fertility effects: Yes

Bendamustine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes 2 weeks before, during treatment, and for at least 4 weeks after the last dose.

- Excretion into breast milk: Unknown
Breastfeeding is not recommended.

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H - Interactions

No clinical assessments of pharmacokinetic drug-drug interactions between bendamustine and other drugs have been conducted. The following are potential interactions with unknown clinical consequence(s). In vitro data suggest bendamustine may be a substrate for P-gp, but is unlikely to affect drug metabolism via CYP1A2, 2C9/10, 2D6, 2E1 or 3A4/5 or induce metabolism of substrates.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)	↑ bendamustine concentration and/or toxicity	↓ metabolism of bendamustine; ↓ formation of active metabolites	Caution
CYP1A2 inducers (e.g. omeprazole, smoking)	↓ bendamustine concentration and/or efficacy; ↑ active metabolites concentration and /or toxicity	↑ metabolism of bendamustine; ↑ formation of active metabolites	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle
Liver function tests	Baseline and regular
Renal function tests	Baseline and regular
Electrolytes, including sodium, potassium, magnesium and uric acid	Baseline and regular

Hepatitis B surface antigen	Baseline and as clinically indicated
Blood pressure	Baseline and before each dose
Clinical toxicity assessment for infection (including CMV and herpes zoster), renal, cardiac, hepatic and skin toxicity , infusion reactions and secondary malignancies	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
HIV status	Baseline
ECG	As clinically indicated; periodic in the setting of cardiac disorders and electrolyte imbalances
Blood glucose	Baseline and periodic
CMV testing in febrile patients	As clinically indicated

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J - Supplementary Public Funding

New Drug Funding Program ([NDFP Website](#))

- Bendamustine - First Line - Chronic Lymphocytic Leukemia
- Bendamustine - Relapsed_Refractory - Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma
- Bendamustine - First Line - Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma
- Polatuzumab Vedotin with Bendamustine and Rituximab (Biosimilar) - Relapsed or Refractory Diffuse Large B-cell Lymphoma

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K - References

Garnock-Jones, K. Bendamustine: a review of its use in the management of indolent Non-Hodgkin's

Lymphoma and Mantle Cell Lymphoma. *Drugs* 2010; 70(13):1703-1718.

Drug Monograph: Treanda® (bendamustine). Lundbeck Canada Inc, February 2017.

Prescribing Information: Treanda® (bendamustine). Cephalon Inc, July 2010.

Van der Jagt R, Laneuville P, MacDonald D, *et al.* A Canadian perspective on bendamustine for the treatment of chronic lymphocytic leukemia and non-Hodgkin lymphoma. *Curr Oncol* 2012; 19(3):160-167.

May 2022 Added NDFP form

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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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