Drug Monograph

A - Drug Name

bendamustine

COMMON TRADE NAME(S): Treanda®

back to top

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-naive 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

back to top

C - Indications and Status

Health Canada Approvals:

- Non-Hodgkin Lymphoma (NHL)
- Chronic lymphocytic leukemia (CLL)

Refer to the product monograph for a full list and details of approved indications.

back to top

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
	Tumour 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.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Hypertension should be controlled prior to starting treatment.

Do not retreat until ANC ≥ 1 x 10^9/L and platelets ≥ 75 x 10^9/L and non-hematologic toxicity has recovered to ≤ 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 ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L then reduce by 1 dose level
≥ Grade 3 Hypersensitivity reaction	Discontinue
≥ Grade 2 clinically significant Non-hematologic toxicities; ≥ Grade 3 Non-hematologic toxicities	Delay until recovered to ≤ grade 1, then reduce by one dose level

Dosage with Hepatic Impairment:

Bilirubin		AST or ALT or ALP	Dose
< 1.5 x ULN	OR	≤ 2.5 x ULN	Caution
> 1.5 x ULN	OR	> 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.

back to top

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.

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components (including mannitol)
- Patients with CrCl < 40 mls/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
- Pregnancy:
  Bendamustine is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners 2 weeks before, during treatment, and for at least **4 weeks** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Yes
  Observed in clinical trials (in patients who can get others pregnant).
  Impaired spermatogenesis has been reported; in some instances, it may return several years after intensive chemotherapy has been discontinued.

back to top

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

back to top

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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

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
Blood pressure	Baseline and before each dose
Clinical toxicity assessment for infection (including CMV and herpes zoster), tumour lysis syndrome, 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

back to top

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

back to top

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.

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

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

Product Monograph: Treanda® (bendamustine). Teva Canada Limited. January 25, 2023.

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.

November 2024 Updated Dosing, Pregnancy and Lactation, and Monitoring sections

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top