

## New Drug Bulletin:

### Bendamustine Hydrochloride (Treanda® - Cephalon, Inc.)

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Bendamustine (Treanda®) is a bifunctional derivative of mechlorethamine. Bendamustine was approved on March 20, 2008 for the treatment of chronic lymphocytic leukemia (CLL). Bendamustine alkylates DNA in both dormant and dividing cells, disrupting DNA synthesis and causing cell death.

Bendamustine is administered intravenously (IV). Plasma concentration peaks at the end of the infusion after a single dose of bendamustine 100 mg/m<sup>2</sup> IV. Mean volume of distribution at steady state is ~25 L. Bendamustine is metabolized by hepatic CYP1A2 to active minor metabolites (M3, M4). Plasma concentrations of these metabolites are a fraction (M3: 10%, M4: 1%) of those of the parent drug. About 90% of the dose is excreted in feces. Clearance is ~700 mL/minute. Terminal elimination half-life is ~40 minutes for bendamustine, 3 hours for M3, and 30 minutes for M4.

One controlled trial is available in 301 treatment-naïve patients with Binet Stage B or C (Rai stages I – IV) CLL. Patients were randomized to either bendamustine 100 mg/m<sup>2</sup> IV on days 1 and 2, or to chlorambucil 0.8 mg/kg orally on days 1 and 15, both given in 28-day cycles. Bendamustine was more effective than chlorambucil, based on higher overall response (bendamustine 59%, chlorambucil 26%,  $p < 0.0001$ ), complete response (bendamustine 8%, chlorambucil < 1%,  $p$  value not reported), and partial response (bendamustine 48%, chlorambucil 25%,  $p$  value not reported). Median progression-free survival was longer with bendamustine (18 months) than chlorambucil (6 months,  $p < 0.0001$ ).

Myelosuppression is common with bendamustine and may be dose-limiting, including neutropenia (any 28%, grade 3/4 24%), thrombocytopenia (23%), anemia (19%), leukopenia (18%), and febrile neutropenia (3%). In the CLL trial, 20% of bendamustine-treated patients required red blood cell transfusions. Other common adverse reactions include increased bilirubin (34%), fever (24%), nausea (20%), vomiting (16%), and infection (6%). Infusion reactions are common with the first dose including fever, chills, itching, or rash. Infusion reactions and severe anaphylactoid reactions occur rarely with subsequent doses. Discontinue bendamustine in patients with severe infusion reactions. In patients with mild reactions to the first infusion, premedicate with antihistamines, antipyretics, and corticosteroids prior to additional doses. Skin reactions have been reported, including rash, toxic skin reactions, and bullous exanthema; interrupt or discontinue bendamustine in patients with severe or progressive reactions. Tumor lysis syndrome may occur, usually during the first treatment cycle. Bendamustine is contraindicated in patients with known hypersensitivity to the drug or any excipients (eg, mannitol), in patients with creatinine clearance less than 40 mL/min, and in patients with moderate or severe hepatic dysfunction.

Drug interactions with bendamustine have not been formally studied. However, bendamustine concentrations may be decreased by drugs that induce CYP1A2 (eg, smoking), although concentrations of M3 and M4 would be increased. CYP1A2 inhibitors (eg,

ciprofloxacin, fluvoxamine) could increase bendamustine concentrations and decrease concentrations of M3 and M4.

The recommended dose is bendamustine 100 mg/m<sup>2</sup> IV, infused over 30 minutes, given on days 1 and 2 of each 28-day cycle for up to 6 cycles. Consider allopurinol prophylaxis when starting therapy in patients at risk for tumor lysis syndrome. Delay subsequent cycles until toxicity resolves in patients with grade  $\geq 2$  non-hematologic toxicity or grade 4 hematologic toxicity. Decrease dose to 50 mg/m<sup>2</sup>/dose for the next cycle in patients with grade  $\geq 3$  toxicity. Further reduce the dose to 25 mg/m<sup>2</sup>/dose if grade  $\geq 3$  toxicity recurs.

Bendamustine is supplied as preservative-free lyophilized powder in single-dose vials containing bendamustine 100 mg and mannitol 170 mg. Store the lyophilized powder at room temperature and protect from light. Reconstitute each vial with 20 mL of Sterile Water for Injection. Transfer the desired dose to 500 mL of 0.9% Sodium Chloride Injection within 30 minutes of reconstitution. Diluted solutions are stable for 24 hours refrigerated or 3 hours at room temperature, including administration time. Table 1 compares the cost of therapy with bendamustine and chlorambucil.

**Table 1. Average Wholesale Price (AWP) of Bendamustine and Chlorambucil for CLL**

Drug / Dosage Form	Dosage Regimen	AWP / Day	AWP / Cycle
Bendamustine (Treanda®) 100 mg vial	100 mg/m <sup>2</sup> IV on days 1 and 2 of each 28-day cycle, or 200 mg/dose in a patient with body surface area of 2 m <sup>2</sup> .	\$4,320	\$8,640
Chlorambucil (Leukeran®) 2 mg tablets	0.8 mg/kg orally on days 1 and 15 of each 28-day cycle, or 56 mg/dose in a patient weighing 70 mg.	\$75	\$151

In summary, bendamustine is an alternative to chlorambucil for the treatment of patients with CLL. Bendamustine improved overall response rate and progression-free survival compared with chlorambucil in a controlled trial.

#### References:

1. Cephalon. Treanda® (bendamustine hydrochloride) for Injection Prescribing Information. In. Frazer, PA; 2008.
2. Murray L, ed. Red Book. Pharmacy's Fundamental Reference, 2008 edition. Montvale, NJ: Thomson PDR; 2008.

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