℞ **BENDAMUSTINE HYDROCHLORIDE**

BENTERO 25/100

25 mg and 100 mg Lyophilized Powder for
Concentrate for Solution for I. V. Infusion

Antineoplastic Agent (Nitrogen Mustard Analogue)

FORMULATION:
Each vial contains:
Bendamustine Hydrochloride Monohydrate (equivalent to Bendamustine Hydrochloride) ..... 25 mg
Bendamustine Hydrochloride Monohydrate (equivalent to Bendamustine Hydrochloride) ..... 100 mg

INDICATIONS:
It is indicated for the treatment of patients with
1. Chronic Lymphocytic Leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established
2. Indolent B-cell Non-Hodgkin Lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

ADVERSE EFFECTS:
Most common non-hematologic adverse reactions for CLL (frequency ≥15%) are pyrexia, nausea, and vomiting.

Most common non-hematologic adverse reactions for NHL (frequency ≥ 15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis.

Most common hematologic abnormalities for both indications (frequency≥ 15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Bendamustine Hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic systems disorders: Pancytopenia

Cardiovascular disorders: Atrial fibrillation, congestive heart failure (some fatal), myocardial infarction (some fatal), palpitation

General disorders and administration site conditions:

Injection site reactions (including phlebitis, pruritus, irritation, pain, swelling), infusion site reactions (including phlebitis, pruritus, irritation, pain, swelling)

Immune system disorders: Anaphylaxis

Infections and infestations: Pneumocystis jiroveci pneumonia.

Respiratory, thoracic and mediastinal disorders: Pneumonitis
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (with concomitant allopurinol and other medications known to cause the syndrome), Toxic epidermal necrolysis (with concomitant allopurinol and other medications known to cause the condition).

INTERACTIONS
Bendamustine is extensively metabolized by cytochrome P450 isoenzyme '**Cytochrome P450 1A2'** (abbreviated **CYP1A2**), such as fluvoxamine and ciprofloxacin, may increase exposure to bendamustine. Conversely, CYP1A2 inducers such as omeprazole can reduce exposure to bendamustine, tobacco smoking also may increase exposure to bendamustine.

Pharmacokinetics
Bendamustine is about 95% bound plasma proteins, data suggest it is not likely to displace nor to be displaced by highly protein-bound drugs. Bendamustine distributes freely into human red blood cells. It is mainly metabolized by hydrolysis via the cytochrome P450 isoenzyme CYP1A2. Little or no accumulation in plasma is anticipated for intravenous doses of bendamustine given on days 1 and 2 of a 28 day cycle. About 90% of the drug is eliminated mainly via the faeces.

DOSAGE AND ADMINISTRATION
For CLL:

- 100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28 day cycle, up to 6 cycles
- Dose modifications for hematologic toxicity: reduce dose to 50mg/m^2 on Days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25mg/m^2 on Days 1 and 2.
- Dose modifications for non- hematologic toxicity : for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle.
- Dose re- escalation may be considered.

For NHL:

- 120 mg/m^2 infused intravenously over 60 minutes on Days 1 and 2 of a 21 Day cycle , up to 8 cycles
- Dose modifications for hematologic toxicity : for Grade 4 toxicity , reduce the dose to 90 mg/m2 on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.
- Dose modifications for non- hematologic toxicity: for Grade 3 greater toxicity, reduce the dose to 90mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

General Dosing Considerations :

- Delay treatment for Grade 4 hematologic or clinically significant ≥Grade 2 non – hematologic toxicity.

ADMINISTRATION IN HEPATIC IMPAIRMENT
Although no meaningful effect on the pharmacokinetic of bendamustine was seen in mild hepatic impairment, data are limited, and therefore caution should be exercised when using bendamustine in these patients. Bendamustine should not be used in moderate or severe hepatic impairment due to a lack of data.

ADMINISTRATION IN RENAL IMPAIRMENT
Although no meaningful effect on the pharmacokinetics of bendamustine was seen in renal impairment, data are limited, and therefore caution should be exercised in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with creatinine clearance less than 40mL/minute, due to a lack of data.

Reconstituted concentrations	Diluents	Solution Stability	Storage condition
0.2 mg/mL concentration	Sodium chloride solution 0.9 %	Initial,3hrs at room temperature, 24 hrs.at 2-8°C	At Room temperature (25°C) & 2-8°C
	Dextrose Solution 2.5%		
0.6 mg/mL concentration	Sodium chloride solution 0.9 %	Initial,3hours, 24 hrs.at 2-8**°C**	
	Dextrose Solution 2.5%		

Direction for Reconstitution:
Add 25 mL of 0.9% NaCl injection (without preservatives) to make a solution. Shake to dissolve. Administer solution within 24 hours.

Size: 100 x 265 mm
Pharma Code No: 8390
Leaflet folding size: 40 x 30 mm
Spec.: Printed on 60 GSM Maplitho paper, Front and Back side printing.
Note: Pharma code position and Orientation are tentative,
will be changed based on folding size.
Color: Black

WARNINGS AND PRECAUTIONS

Myelosuppression: Delay or reduce dose. Restart treatment based on Absolute Neutrophil Count (ANC) and platelet count recovery. Complications of myelosuppression may lead to death.

Infections :Monitor for fever and other signs of infection or reactivation of infections and treat promptly.

Anaphylaxis and Infusion Reactions: Severe and anaphylactic reactions have occurred; monitor clinically and discontinue Bendamustine Hydrochloride. Premedicate in subsequent cycles for milder reactions.

Tumor Lysis Syndrome : Acute renal failure and death; anticipate and use supportive measures.

Skin Reactions: Discontinue for severe skin reactions. Cases of Stevens-Johnson Syndrome (SJS) and toxic Epidermal Necrolysis (TEN), some fatal, have been reported when Bendamustine Hydrochloride was administered concomitantly with allopurinol and medications known to cause these Syndromes

Other Malignancies; Pre-malignant diseases have been reported.

Extravasation Injury: Assure good venous access and monitor infusion site during an after administration

Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving Bendamustine Hydrochloride.

USE IN SPECIFIC POPULATIONS

Renal Impairment:

Do not use if Creatinine Clearance (CrCl) is <40 ml/min. Use with caution in lesser degrees of renal impairment.

Hepatic Impairment:

Do not use in moderate or severe hepatic impairment. Use with caution in mild hepatic impairment

Pregnancy

Bendamustine Hydrochloride can cause fetal harm when administered to a pregnant woman. Bendamustine caused malformations in animals, when a single dose was administered to pregnant animals. Advise women to avoid becoming pregnant while receiving Bendamustine Hydrochloride and for 3 months after therapy has stopped. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to a fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for bendamustine in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The effectiveness of bendamustine in pediatric patients has not been established. Bendamustine was evaluated in a single Phase 1/2 trial in pediatric patients with leukemia. The safety profile for bendamustine in pediatric patients was consistent with that seen in adults, and no new safety signals were identified.

Geriatric Use

In CLL and NHL studies, there were no clinically significant differences in the adverse reaction profile between geriatric (≥65 years of age) and younger patients.

STORAGE AND HANDLING

Safe Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from bendamustine hydrochloride for injection. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of bendamustine hydrochloride for injection contacts the skin, wash the skin immediately and thoroughly with soap and water. If bendamustine hydrochloride for injection contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered.

AVAILABILITY

25 mg: 10 mL-capacity USP Type I amber glass vial with gray bromo butyl rubber stopper and aluminum seal with blue colored plastic flip-off cap (Box of 1 's)

100 mg: Type 1 amber glass vial with gray colour 20 mm bromo butyl rubber stopper and blue colour 20 mm flip off seal (Box of 1 's)

STORAGE CONDITION

Store at temperatures not exceeding 30°C. Protect from light and moisture.

STABILITY

Once reconstituted as directed and further diluted with sodium chloride 0.9%, the final infusion solution is stable for 24 hours when refrigerated (2 deg to 8 deg) or for 3 hours when stored at room temperature (15 deg to 30 deg) and exposed to light.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT: For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction.

Manufactured by:

HETERO

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