BENDAMAX

Bendamustine Hydrochloride

COMPOSITION
Bendamax Injection: Each vial contains Bendamustine INN 25 mg

CLINICAL PHARMACOLOGY
Description:
Bendamax contains Bendamustine Hydrochloride, an alkylating drug, as the active ingredient. The chemical name of Bendamustine Hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride. Its empirical molecular formula is C16H21Cl2N3O2 · HCl, and the molecular weight is 394.7.

Mechanism of Action
Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of Bendamustine remains unknown.

Pharmacodynamics
Absorption: Following a single IV dose of Bendamustine Hydrochloride Cmax typically occurred at the end of infusion. The dose proportionality of Bendamustine has not been studied.

Distribution: In vitro, the binding of Bendamustine to human serum plasma proteins ranged from 94-96% and was concentration independent from 1-50 ?g/mL. Data suggest that Bendamustine is not likely to displace or to be displaced by highly protein-bound drugs. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 ?g/mL indicating that Bendamustine distributes freely in human red blood cells. In humans, the mean steady state volume of distribution (Vss) was approximately 25 L.

Metabolism: In vitro data indicate that Bendamustine is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. In vitro, studies indicate that two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are 1/10 and 1/100 that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to Bendamustine.

In vitro studies using human liver microsomes indicate that Bendamustine does not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 enzymes in primary cultures of human hepatocytes.

Elimination: No mass balance study has been undertaken in humans. Preclinical radiolabeled Bendamustine studies showed that approximately 90% of drug administered was recovered in excreta primarily in the feces.

Bendamustine clearance in humans is approximately 700 mL/minute. After a single dose of 120 mg/m2 Bendamustine IV over 1-hour the intermediate t½ of the parent compound is approximately 40 minutes. The mean apparent terminal elimination t½ of M3 and M4 are approximately 3 hours and 30 minutes respectively. Little or no accumulation in plasma is expected for Bendamustine administered on Days 1 and 2 of a 28-day cycle.

Renal Impairment: In a population pharmacokinetic analysis of Bendamustine in patients receiving 120 mg/m2 there was no meaningful effect of renal impairment (CrCL 40 - 80 mL/min, N=31) on the pharmacokinetics of Bendamustine. Bendamustine has not been studied in patients with CrCL < 40 mL/min. These results are however limited, and therefore Bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < 40 mL/min.

Hepatic Impairment: In a population pharmacokinetic analysis of Bendamustine in patients receiving 120 mg/m2 there was no meaningful effect of mild (total bilirubin ? ULN, AST ? ULN to 2.5 x ULN, and/or ALP ? ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of Bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment. These results are however limited, and therefore Bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5 - 10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment.

CLINICAL INFORMATION
Therapeutic Indication

Chronic Lymphocytic Leukemia (CLL)
BENDAMAX® is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.

Non-Hodgkin's Lymphoma (NHL)
BENDAMAX for Injection is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with Rituximab or a Rituximab-containing regimen.

DOSAGE AND ADMINISTRATION

Dosing Instructions for CLL

Recommended Dosage: The recommended dose is 100 mg/m2 administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

Dose Delays, Dose Modifications and Reinitiation of Therapy for CLL: BENDAMAX administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant ? Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ? Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ? 1 x 109/L, platelets ? 75 x 109/L], BENDAMAX can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted.

Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m2 on Days 1 and 2 of each cycle.

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

Dosing Instructions for NHL

Recommended Dosage: The recommended dose is 120 mg/m2 administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Dose Delays, Dose Modifications and Reinitiation of Therapy for NHL: BENDAMAX administration should be delayed in the event of a Grade 4 hematologic toxicity or clinically significant ? Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ? Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ? 1 x 109/L, platelets ? 75 x 109/L], BENDAMAX can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted.

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/m2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m2 on Days 1 and 2 of each cycle.

General Considerations for Tumor Lysis Syndrome Consider using allopurinol as prevention for patients at high risk of tumor lysis syndrome for the first few weeks of treatment.

RECONSTITUTION/PREPARATION FOR INTRAVENOUS ADMINISTRATION
Aseptically reconstitute each 25 mg BENDAMAX vial with 5 mL of only Sterile Water for Injection, USP. Shake well to yield a clear, colorless to a pale yellow solution with a Bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. If particulate matter is observed, the reconstituted product should not be used.

Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and immediately transfer to a 100 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of Bendamustine HCl in the infusion bag should be within 0.2 - 0.6 mg/mL. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colorless to slightly yellow solution.

Use Sterile Water for Injection, USP, for reconstitution and then either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Any unused solution should be discarded according to institutional procedures for antineoplastics.

Admixture Stability
BENDAMAX contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration.

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of BENDAMAX must be completed within this period.

CONTRAINDICATIONS
BENDAMAX is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to Bendamustine or mannitol.

OVERDOSE
The intravenous LD50 of Bendamustine HCl is 240 mg/m2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

Across all clinical experience, the reported maximum single dose received was 280 mg/m2. Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients) and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients.

No specific antidote for BENDAMAX overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

WARNINGS AND PRECAUTIONS
Myelosuppression
Patients treated with BENDAMAX are likely to experience myelosuppression. In the two NHL studies, 98% of patients had Grade 3-4 myelosuppression (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils closely. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Hematologic nadirs may require dose delays if recovery to the recommended values have not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be ? 1 x 109/L and the platelet count should be ? 75 x 109/L.

Infections
Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with BENDAMAX are more susceptible to infections. Patients with myelosuppression following BENDAMAX treatment should be advised to contact a physician if they have symptoms or signs of infection.

Infusion Reactions and Anaphylaxis
Infusion reactions to BENDAMAX have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.

Tumor Lysis Syndrome
Tumor lysis syndrome associated with BENDAMAX treatment has been reported in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of BENDAMAX and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, close monitoring of blood chemistry, particularly potassium and uric acid levels, and the use of allopurinol during the first few weeks of BENDAMAX therapy in patients at high risk.

Skin Reactions
A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when BENDAMAX was given in combination with other anticancer agents, so the precise relationship to BENDAMAX is uncertain. In a study of Bendamustine (90 mg/m2) in combination with Rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for Rituximab. The relationship to BENDAMAX cannot be determined. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are severe or progressive, BENDAMAX should be withheld or discontinued.

Other Malignancies
There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with BENDAMAX, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with BENDAMAX therapy has not been determined.

ADVERSE EFFECTS
The data described below reflect exposure to BENDAMAX in 349 patients who participated in an actively-controlled trial (N=153) for the treatment of CLL and two single-arm studies (N=176) for the treatment of indolent B-cell NHL. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following serious adverse reactions have been associated with BENDAMAX in clinical trials and are discussed in greater detail in other sections of the label.

- Myelosuppression
- Infections
- Infusion Reactions and Anaphylaxis
- Tumor Lysis Syndrome
- Skin Reactions
- Other Malignancies

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category D

BENDAMAX can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the 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 safety and effectiveness of BANDAMAX in pediatric patients have not been established.

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.

PHARMACEUTICAL INFORMATION
Storage condition
Store the vial in original carton below 30°C. Protect from light and keep out of the reach of children.
Reconstitute Bendamax with 5 ml. Sterile Water for Injection, USP Bendamusine HCl concentration in the reconstituted solution is 5 mg/ml. Requires immediate further dilution. Use the final solution within 24 hours when stored refrigerated (2° to 8°C) or within 3 hours when stored at room temperature (below 30°C). Protect from light and keep out of the reach of children.

Presentation & Packaging
Bendamax Injection: Each commercial box contains 1 vial of Bendamax INN 25 mg.

Manufactured By
BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

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