CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BENDEKA safely and effectively. See full prescribing information for BENDEKA.

BENDEKA™ (bendamustine hydrochloride) Injection, for intravenous use.
Initial U.S. Approval: 2008

----------INDICATIONS AND USAGE----------
Bendamustine hydrochloride is an alkylating drug indicated for treatment of patients with:
- Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. (1.1)
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. (1.2)

----------DOSAGE AND ADMINISTRATION----------
For CLL:
- 100 mg/m^2 infused intravenously over 10 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles (2.1)
- Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce dose to 50 mg/m^{2}on Days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m^2 on Days 1 and 2. (2.1)
- 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. (2.1)
- Dose re-escalation may be considered. (2.1)

For NHL:
- 120 mg/m^2 infused intravenously over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles (2.2)
- Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m^2 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. (2.2)
- Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/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. (2.2)

General Dosing Considerations:
- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. (2.1, 2.2)
- BENDEKA must be diluted prior to infusion. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 100 mg/4 mL (25 mg/mL) in a multiple-dose vial (3).

----------CONTRAINDICATIONS----------
- BENDEKA is contraindicated in patients with a history of a hypersensitivity reaction to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol. Reactions to bendamustine hydrochloride have included anaphylaxis and anaphylactoid reactions (4, 5.3)

----------WARNINGS AND PRECAUTIONS----------
- Myelosuppression: Delay or reduce dose. Restart treatment based on ANC and platelet count recovery. (2.1) Complications of myelosuppression may lead to death. (5.1)
- Infections: Monitor for fever and other signs of infection and treat promptly. (5.2)
- Anaphylaxis and Infusion Reactions: Severe anaphylactic reactions have occurred. Monitor clinically and discontinue drug for severe reactions. Pre-medicate in subsequent cycles for milder reactions. (5.3)
- Tumor Lysis Syndrome: May lead to acute renal failure and death; anticipate and use supportive measures in patients at high risk. (5.4)
- Skin Reactions: Discontinue for severe skin reactions. Cases of SJS and TEN, some fatal, have been reported when bendamustine hydrochloride was administered concomitantly with allopurinol and other medications known to cause these syndromes. (5.5)
- Other Malignancies: Pre-malignant and malignant diseases have been reported. (5.6)
- Extravasation: Take precautions to avoid extravasation, including monitoring intravenous infusion site during and after administration. (5.7)
- 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. (5.8, 8.1)

----------ADVERSE REACTIONS----------
- Adverse reactions (frequency >5%) during infusion and within 24 hours post-infusion are nausea and fatigue (6.1)
- Most common non-hematologic adverse reactions for CLL (frequency ≥15%) are pyrexia, nausea, and vomiting. (6.2)
- 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. (6.3)
- Most common hematologic abnormalities (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. (6.2, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Eagle Pharmaceuticals, Inc. at 1-855-318-2170 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------DRUG INTERACTIONS----------
Concomitant CYP1A2 inducers or inhibitors have the potential to affect the exposure of bendamustine. (7)

----------USE IN SPECIFIC POPULATIONS----------
- Renal impairment: Do not use if CrCL is <40 mL/min. Use with caution in lesser degrees of renal impairment. (8.6)
- Hepatic impairment: Do not use in moderate or severe hepatic impairment. Use with caution in mild hepatic impairment. (8.7)

***See* 17 for PATIENT COUNSELING INFORMATION**

Revised: 12/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

BENDEKA (bendamustine hydrochloride) Injection is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.

1.2 Non-Hodgkin Lymphoma (NHL)

BENDEKA (bendamustine hydrochloride) Injection is indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions for CLL

Recommended Dosage:
The recommended dose is 100 mg/m^2 administered intravenously over 10 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:
BENDEKA (bendamustine hydrochloride) Injection administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant greater than or equal to Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to less than or equal to Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) greater than or equal to 1 x 10^9/L, platelets greater than or equal to 75 x 10^9/L], BENDEKA (bendamustine hydrochloride) Injection can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. [*see Warnings and Precautions (5.1)*]

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

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

2.2 Dosing Instructions for NHL

Recommended Dosage:
The recommended dose is 120 mg/m^2 administered intravenously over 10-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:
BENDEKA (bendamustine hydrochloride) Injection administration should be delayed in the event of a Grade 4 hematologic toxicity or clinically significant greater than or equal to Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to less than or equal to Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) greater than or equal to 1 x 10^9/L, platelets greater than or equal to 75 x 10^9/L], BENDEKA (bendamustine

hydrochloride) Injection can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. [*see Warnings and Precautions (5.1)*]

Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m^2 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 or greater toxicity, reduce the dose to 90 mg/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.

2.3 Preparation for Intravenous Administration

BENDEKA (bendamustine hydrochloride) Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

BENDEKA is in a multiple-dose vial. BENDEKA is a clear, and colorless to yellow ready-to-dilute solution. Allow vial to reach room temperature. If particulate matter is observed, the product should not be used.

Intravenous Infusion

- Aseptically withdraw the volume needed for the required dose from the 25 mg/mL solution as per Table A below and immediately transfer the solution to a 50 mL infusion bag of one of the following diluents:
  - 0.9% Sodium Chloride Injection, USP; or
  - 2.5% Dextrose/0.45% Sodium Chloride Injection, USP; or
  - 5% Dextrose Injection, USP.

The resulting final concentration of bendamustine hydrochloride in the infusion bag should be within 1.85 mg/mL – 5.6 mg/mL. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear, and colorless to yellow solution.

No other diluents have been shown to be compatible. The 5% Dextrose Injection, USP, offers a sodium-free method of administration for patients with certain medical conditions requiring restricted sodium intake.

Table A: Volume (mL) of BENDEKA required for dilution into 50 mL of 0.9% saline, or 0.45% saline/2.5% dextrose or 5% dextrose for a given dose (mg/m^2) and Body Surface Area (m^2)

Body Surface Area (m^2)	Volume of BENDEKA to withdraw (mL)					
	120 mg/m^2	100 mg/m^2	90 mg/m^2	60 mg/m^2	50 mg/m^2	25 mg/m^2
1	4.8	4	3.6	2.4	2	1
1.1	5.3	4.4	4	2.6	2.2	1.1
1.2	5.8	4.8	4.3	2.9	2.4	1.2
1.3	6.2	5.2	4.7	3.1	2.6	1.3
1.4	6.7	5.6	5	3.4	2.8	1.4

Body Surface Area (m^2)	Volume of BENDEKA to withdraw (mL)					
	120 mg/m^2	100 mg/m^2	90 mg/m^2	60 mg/m^2	50 mg/m^2	25 mg/m^2
1.5	7.2	6	5.4	3.6	3	1.5
1.6	7.7	6.4	5.8	3.8	3.2	1.6
1.7	8.2	6.8	6.1	4.1	3.4	1.7
1.8	8.6	7.2	6.5	4.3	3.6	1.8
1.9	9.1	7.6	6.8	4.6	3.8	1.9
2	9.6	8	7.2	4.8	4	2
2.1	10.1	8.4	7.6	5	4.2	2.1
2.2	10.6	8.8	7.9	5.3	4.4	2.2
2.3	11	9.2	8.3	5.5	4.6	2.3
2.4	11.5	9.6	8.6	5.8	4.8	2.4
2.5	12	10	9	6	5	2.5
2.6	12.5	10.4	9.4	6.2	5.2	2.6
2.7	13	10.8	9.7	6.5	5.4	2.7
2.8	13.4	11.2	10.1	6.7	5.6	2.8
2.9	13.9	11.6	10.4	7	5.8	2.9
3	14.4	12	10.8	7.2	6	3

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.

2.4 Admixture Stability

BENDEKA (bendamustine hydrochloride) Injection contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration.

If diluted with 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 36-46°F) or for 6 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA (bendamustine hydrochloride) Injection must be completed within this period of time.

In the event that 5% Dextrose Injection, USP is utilized, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for only 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA must be completed within this period of time.

Retain the partially used vial in original package to protect from light and store refrigerated (2-8°C or 36-46°F) if additional dose withdraw from the same vial is intended.

2.5 Stability of Partially Used Vials (Needle Punched Vials)

BENDEKA is supplied in a multiple-dose vial. Although it does not contain any antimicrobial preservative, BENDEKA is bacteriostatic. The partially used vials are stable for up to 28 days

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