

## 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

BENDEKA injection 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<sup>2</sup> infused intravenously over 10 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. (2.1)

#### For NHL:

- 120 mg/m<sup>2</sup> infused intravenously over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. (2.2)

### 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 monoethioglycerol. Reactions to bendamustine hydrochloride have included anaphylaxis and anaphylactoid reactions (4, 5.3)

### WARNINGS AND PRECAUTIONS

- Myelosuppression: Delay or reduce dose, and restart treatment based on ANC and platelet count recovery. (2.1, 5.1)
- Infections: Monitor for fever and other signs of infection or reactivation of infections 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, DRESS and TEN, some fatal, have been reported. (5.5)
- Hepatotoxicity: Monitor liver chemistry tests prior to and during treatment. (5.6)
- Other Malignancies: Pre-malignant and malignant diseases have been reported. (5.7)
- Extravasation Injury: Take precautions to avoid extravasation, including monitoring intravenous infusion site during and after administration. (5.8)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception. (5.9, 8.1, 8.3)

### ADVERSE REACTIONS

- Adverse reactions (frequency >5%) during infusion and within 24 hours post-infusion are nausea and fatigue. (6.1)
- Most common adverse reactions (≥15%) for CLL are anemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, hyperbilirubinemia, pyrexia, nausea, vomiting. (6.2, 6.3)
- Most common adverse reactions (≥15%) for NHL are lymphopenia, leukopenia, anemia neutropenia, thrombocytopenia, nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis.(6.2, 6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>

### DRUG INTERACTIONS

Consider alternative therapies that are not CYP1A2 inducers or inhibitors during treatment with BENDEKA. (7.1)

### USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Infertility: May impair fertility. (8.3)
- Renal Impairment: Do not use in patients with creatinine clearance <30 mL/min. (8.6)
- Hepatic Impairment: Do not use in patients with total bilirubin 1.5-3 × ULN and AST or ALT 2.5-10 × ULN, or total bilirubin > 3 × ULN. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Chronic Lymphocytic Leukemia (CLL)

BENDEKA<sup>®</sup> is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to fludarabine or chlorambucil has not been established.

#### 1.2 Non-Hodgkin Lymphoma (NHL)

BENDEKA is indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed after 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<sup>2</sup> administered intravenously over 10 minutes on Days 1 and 2 of a 28-day cycle.

##### Dose Delays, Dose Modifications and Reinitiation of Therapy for CLL:

Delay BENDEKA administration in the event of Grade 4 hematologic toxicity or clinically significant greater than Grade 3 non-hematologic toxicity. Once non-hematologic toxicity has recovered to less than or equal to Grade 1 and/or toxicity has improved [Absolute Neutrophil Count (ANC) greater than or equal to 1 x 10<sup>9</sup>/L, platelets greater than or equal to 100,000/mm<sup>3</sup>], reinitiate BENDEKA (bendamustine hydrochloride) injection at the discretion of the treating physician. In addition, consider dose reduction. [see *Warnings and Precautions* (5.1)]

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

Consider dose re-escalation in subsequent cycles at the discretion of the treating physician.

## 2.2 Dosing Instructions for NHL

### Recommended Dosage:

The recommended dose is 120 mg/m<sup>2</sup> administered intravenously over 10 minutes on Days 1 and 2 of a 21-day cycle.

### Dose Delays, Dose Modifications and Reinitiation of Therapy for NHL:

Delay BENDEKA administration 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 laboratory values have improved [Absolute Neutrophil Count (ANC) greater than or equal to 1 x 10<sup>9</sup>/L, platelets greater than or equal to 100 x 10<sup>9</sup>/L], reinitiate BENDEKA at the discretion of the treating physician. In addition, consider dose reduction. [see [Warnings and Precautions \(5.1\)](#)]

Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m<sup>2</sup> on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m<sup>2</sup> 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<sup>2</sup> on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m<sup>2</sup> on Days 1 and 2 of each cycle.

## 2.3 Preparation for Intravenous Administration

BENDEKA is a cytotoxic drug. Follow applicable special handling and disposal procedures.<sup>1</sup>

BENDEKA is in a multiple-dose vial. At room temperature, BENDEKA is a clear, and colorless to yellow ready to use solution. Store BENDEKA at recommended refrigerated storage conditions (2-8°C or 36-46°F). When refrigerated, the contents may freeze. Allow the vial to reach room temperature (15-30°C or 59-86°F) prior to use. Do not use the product if particles are observed after achieving room temperature.

### Intravenous Infusion

- Aseptically withdraw the volume needed for the required dose from the 25 mg/mL solution as per Table A below, and 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. After preparing and 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 met 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 for a given dose (mg/m<sup>2</sup>) and Body Surface Area (m<sup>2</sup>)**

Body Surface Area (m <sup>2</sup> )	Volume of BENDEKA to withdraw (mL)				
	120 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	90 mg/m <sup>2</sup>	60 mg/m <sup>2</sup>	50 mg/m <sup>2</sup>
1	4.8	4	3.6	2.4	2
1.1	5.3	4.4	4	2.6	2.2
1.2	5.8	4.8	4.3	2.9	2.4
1.3	6.2	5.2	4.7	3.1	2.6
1.4	6.7	5.6	5	3.4	2.8
1.5	7.2	6	5.4	3.6	3
1.6	7.7	6.4	5.8	3.8	3.2
1.7	8.2	6.8	6.1	4.1	3.4
1.8	8.6	7.2	6.5	4.3	3.6
1.9	9.1	7.6	6.8	4.6	3.8
2	9.6	8	7.2	4.8	4
2.1	10.1	8.4	7.6	5	4.2
2.2	10.6	8.8	7.9	5.3	4.4
2.3	11	9.2	8.3	5.5	4.6
2.4	11.5	9.6	8.6	5.8	4.8
2.5	12	10	9	6	5
2.6	12.5	10.4	9.4	6.2	5.2
2.7	13	10.8	9.7	6.5	5.4
2.8	13.4	11.2	10.1	6.7	5.6
2.9	13.9	11.6	10.4	7	5.8
3	14.4	12	10.8	7.2	6

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

#### **2.4 Admixture Stability**

BENDEKA contains no antimicrobial preservative. Prepare the admixture 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 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 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 further withdrawal 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 when stored in its original carton under refrigeration (2-8°C or 36-46°F). Each vial is not recommended for more than a total of six (6) dose withdrawals.

After first use, store the partially used vial in the refrigerator in the original carton at 2°-8°C or 36-46°F and then use within 28 days.

### **3 DOSAGE FORMS AND STRENGTHS**

Injection: 100 mg/4 mL (25 mg/mL) as a clear and colorless to yellow ready-to-dilute solution in a multiple-dose vial.

### **4 CONTRAINDICATIONS**

BENDEKA is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol. [see *Warnings and Precautions* (5.1)]

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