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

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.3)	10/2021
Warnings and Precautions (5.3)	10/2021
Warnings and Precautions (5.8)	10/2021

----------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^2 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^2 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 monothioglycerol. Reactions to bendamustine hydrochloride have included anaphylaxis and anaphylactoid reactions (4, 5.4)

----------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)
- Progressive multifocal leukoencephalopathy (PML): Monitor for new or worsening neurological, cognitive or behavioral signs or symptoms suggestive of PML. (5.3)
- 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. (5.4)
- Tumor Lysis Syndrome: May lead to acute renal failure and death; anticipate and use supportive measures in patients at high risk. (5.5)
- Skin Reactions: Discontinue for severe skin reactions. Cases of SJS, DRESS and TEN, some fatal, have been reported. (5.6).
- Hepatotoxicity: Monitor liver chemistry tests prior to and during treatment. (5.7)
- Other Malignancies: Pre-malignant and malignant diseases have been reported. (5.8)
- Extravasation Injury: Take precautions to avoid extravasation, including monitoring intravenous infusion site during and after administration. (5.9)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of the potential risk to a fetus and to use an effective method of contraception. (5.10, 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. (6.1)
- 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.(6.1).

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**

Revised: 10/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

BENDEKA® 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 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 dosage 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, Dosage Modifications and Reinitiation of Therapy for CLL:
Delay BENDEKA administration 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], reinitiate BENDEKA (bendamustine hydrochloride) injection at the discretion of the treating physician. In addition, consider dose reduction. [*see Warnings and Precautions (5.1)*]

Dosage 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.

Dosage 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.

Consider dosage 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^2 administered intravenously over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Dose Delays, Dosage 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 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], reinitiate BENDEKA at the discretion of the treating physician. In addition, consider dose reduction. *[see Warnings and Precautions (5.1)]*

Dosage 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.

Dosage 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 is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

BENDEKA is in a multiple-dose vial. At room temperature, BENDEKA is a clear, and colorless to yellow ready-to-dilute solution. Store BENDEKA at recommended refrigerated storage conditions (2°C to 8°C or 36°F to 46°F). When refrigerated, the contents may freeze. Allow the vial to reach room temperature (15°C to 30°C or 59°F to 86°F) prior to use. Do not use the product if particulate matter is 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 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 0.49 mg/mL to 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
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 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 final admixture is stable for 24 hours when stored refrigerated (2°C to 8°C or 36°F to 46°F) or for 6 hours when stored at room temperature (15°C to 30°C or 59°F to 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°C to 8°C or 36°F to 46°F) or for only 3 hours when stored at room temperature (15°C to 30°C or 59°F to 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°C to 8°C or 36°F to 46°F) if additional dose 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°C to 8°C or 36°F to 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°C to 8°C or 36°F to 46°F and then discard after 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 (5.4)]*

DOCKET ALARM

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