

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

Warnings and Precautions, Infections (5.2) 2/2016
Dosage and Administration (2.3) 6/2016

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/m² 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/m² on Days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m² 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/m² on Days 1 and 2 of each cycle. (2.1)
- Dose re-escalation may be considered. (2.1)

For NHL:

- 120 mg/m² 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/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. (2.2)
- 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. (2.2)

General Dosing Considerations:

- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. (2.1, 2.2)
- Store BENDEKA at recommended refrigerated storage conditions (2-8° C or 36-46° F). When refrigerated the contents may partially freeze. Allow the vial to reach room temperature (15-30° C or 59-89° F) prior to use. (2.3)
- 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 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 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 Injury: 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 Teva Pharmaceuticals at 1-888-483-8279 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: 06/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Chronic Lymphocytic Leukemia (CLL)
- 1.2 Non-Hodgkin Lymphoma (NHL)

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Instructions for CLL
- 2.2 Dosing Instructions for NHL
- 2.3 Preparation for Intravenous Administration
- 2.4 Admixture Stability
- 2.5 Stability of Partially Used Vials (Needle Punched Vials)

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Myelosuppression
- 5.2 Infections
- 5.3 Anaphylaxis and Infusion Reactions
- 5.4 Tumor Lysis Syndrome
- 5.5 Skin Reactions
- 5.6 Other Malignancies
- 5.7 Extravasation Injury

- 6.1 Adverse Events in Clinical Trials
- 6.2 Clinical Trials Experience in CLL
- 6.3 Clinical Trials Experience in NHL
- 6.4 Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Effect of Gender

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

16.2 How Supplied

16.3 Storage

*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 (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/m² 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 10⁹/L, platelets greater than or equal to 75 x 10⁹/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/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.

2.2 Dosing Instructions for NHL

Recommended Dosage:

The recommended dose is 120 mg/m² 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 $1 \times 10^9/L$, platelets greater than or equal to $75 \times 10^9/L$], 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. At room temperature, BENDEKA is a clear, and colorless to yellow ready-to-dilute solution. Store BENDEKA at recommended refrigerated storage conditions ($2-8^\circ \text{C}$ or $36-46^\circ \text{F}$). When refrigerated the contents may partially freeze. Allow the vial to reach room temperature ($15-30^\circ \text{C}$ or $59-86^\circ \text{F}$) prior to use. If particulate matter is observed after achieving room temperature, 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 $1.85 \text{ mg/mL} - 5.6 \text{ mg/mL}$. 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

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 (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 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, the partially used vial should be stored in the refrigerator in the original carton at 2°C to 8°C or 36-46°F and then discarded 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 (bendamustine hydrochloride) Injection 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 (5.3)*]

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Bendamustine hydrochloride caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies (*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).

BENDEKA (bendamustine hydrochloride) Injection causes myelosuppression. Monitor complete blood counts, including leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs occurred predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has 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 $\geq 1 \times 10^9/L$ and the platelet count should be $\geq 75 \times 10^9/L$. [*see Dosage and Administration (2.1)*]

5.2 Infections

Infection, including pneumonia, sepsis, septic shock, hepatitis and death have occurred in adult and pediatric patients in clinical trials and in postmarketing reports for bendamustine hydrochloride. Patients with myelosuppression following treatment with bendamustine hydrochloride are more susceptible to infections. Advise patients with myelosuppression following BENDEKA (bendamustine hydrochloride) Injection treatment to contact a physician immediately if they have symptoms or signs of infection.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.