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

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

----------INDICATIONS AND USAGE----------
BELRAPZO 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 30 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 60 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 or greater non-hematologic toxicity. (2.1, 2.2)

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

----------CONTRAINDICATIONS----------
BELRAPZO 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 bendamustine hydrochloride . Pre-medicate in subsequent cycles for milder reactions. (5.3)
- Tumor Lysis Syndrome: Acute renal failure and death; anticipate and use supportive measures. (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: Assure good venous access and monitor infusion site during and after administration. (5.8)
- 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. (5.9, 8.1)

----------ADVERSE REACTIONS----------
- Most common non-hematologic adverse reactions for CLL (frequency ≥15%) are pyrexia, nausea, and vomiting. (6.1)
- 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. (6.2)
- Most common hematologic abnormalities (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Eagle Pharmaceuticals, Inc. at 1-855-318-2170 or FDA at 1-800-FDA-1088 or *http://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 less than 30 mL/min. (8.6)
- Hepatic Impairment: Do not use in moderate or severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2018

FULL PRESCRIBING INFORMATION: CONTENTS

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

BELRAPZO 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)

BELRAPZO 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 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:

BELRAPZO administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant Grade 2 or greater 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 10^9/L, platelets ≥ 75 x 10^9/L], BELRAPZO 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 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:
BELRAPZO 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 10^9/L, platelets ≥ 75 x 10^9/L], BELRAPZO 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

BELRAPZO is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

BELRAPZO is a clear and colorless to yellow solution. Store BELRAPZO at recommended refrigerated storage conditions (2° to 8°C or 36° to 46°F). When refrigerated the contents may partially freeze. Allow the vial to reach room temperature (15° to 30°C or 59° to 86°F) prior to use. Observe the contents of the vial for any visible solid or particulate matter. Do not use the product if solid or particulate matter is observed after reaching room temperature.

Intravenous Infusion

Aseptically withdraw the volume needed for the required dose (based on 25 mg/mL concentration) as per Table A below and immediately transfer to a **500 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 – 0.7 mg/mL.** After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colorless to slightly yellow solution.

Use 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.

Table A: Volume (mL) of BELRAPZO required for dilution into 500 mL of 0.9% Saline, or 0.45% Saline/2.5% Dextrose for a given dose (mg/m^2) and Body Surface Area (m^2)

Body Surface Area (m^2)	Volume of BELRAPZO 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

Body Surface Area (m^2)	Volume of BELRAPZO 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
1.8	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

General Information

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

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

Once 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 under refrigerated (2° to 8°C or 36° to 46°F) or for 3 hours when stored at room temperature (15° to 30°C or 59° to 86°F) and room light. Administration of diluted BELRAPZO must be completed within this period of time. BELRAPZO (bendamustine hydrochloride injection) is supplied in a multiple-dose vial. Retain the partially used vial in original package to protect from light and store refrigerated (2° to 8°C or 36° to 46°F) if additional dose withdrawal from the same vial is intended.

2.5 Stability of Partially Used Vials (Needle Punched Vials)

BELRAPZO is supplied as a multiple-dose vial. Although it does not contain any antimicrobial preservative, BELRAPZO is bacteriostatic and does not support bacterial growth. The partially used vials are stable for up to 28 days when stored in its original carton under refrigeration (2° to 8°C or 36° to 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 original carton at 2° to 8°C (36° to 46°F), and then discarded after 28 days.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) of bendamustine hydrochloride as a clear solution in a multiple-dose vial.

4 CONTRAINDICATIONS

BELRAPZO 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).

In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed 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) and (2.2)]*

5.2 Infections

Infection, including pneumonia, sepsis, septic shock, hepatitis and death has 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 BELRAPZO treatment to contact a physician immediately if they have symptoms or signs of infection.

Patients treated with bendamustine hydrochloride are at risk for reactivation of infections including (but not limited to) hepatitis B, cytomegalovirus, Mycobacterium tuberculosis, and herpes zoster. Patients should undergo appropriate measures (including clinical and laboratory monitoring, prophylaxis, and treatment) for infection and infection reactivation prior to administration.

5.3 Anaphylaxis and Infusion Reactions

Infusion reactions to bendamustine hydrochloride 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. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experience Grade 3 or worse allergic-type reactions should not be rechallenged. Consider measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids in

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