BENDAMUSTINE HYDROCHLORIDE - bendamustine hydrochloride injection, powder, lyophilized, for solution
Eugia US LLC

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

BENDAMUSTINE HYDROCHLORIDE for injection, for intravenous use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

Bendamustine hydrochloride for 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

Bendamustine hydrochloride for injection is available as a lyophilized powder. (2)

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 (2.2)

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 (2.3)

DOSAGE FORMS AND STRENGTHS

25 mg or 100 mg lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

Bendamustine hydrochloride is contraindicated in patients with a history of a hypersensitivity reaction to bendamustine. Reactions 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. (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 and 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 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, pyrexia, nausea, vomiting. (6.1, 6.2)
- 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, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Eugia US LLC at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Consider alternative therapies that are not CYP1A2 inducers or inhibitors during treatment with bendamustine hydrochloride. (7)

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 to 3 x ULN and AST or ALT 2.5 to 10 x ULN, or total bilirubin >3 x ULN. (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2023

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)

Bendamustine hydrochloride for 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)

Bendamustine hydrochloride for 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 Selection of Bendamustine Hydrochloride for Injection Formulation to Administer

Bendamustine hydrochloride is available in two formulations, a solution (bendamustine

hydrochloride injection) and a lyophilized powder (bendamustine hydrochloride for injection).

Bendamustine hydrochloride injection and the reconstituted bendamustine hydrochloride for injection have different concentrations of bendamustine hydrochloride. The concentration of bendamustine hydrochloride in the solution is 90 mg/mL and the concentration of bendamustine hydrochloride in the reconstituted solution of lyophilized powder is 5 mg/mL. **Do not mix or combine the two formulations.**

If a closed system transfer device (CSTD) or adapter that contains polycarbonate or acrylonitrilebutadiene-styrene (ABS) is used as supplemental protection prior to dilution[1], only use bendamustine hydrochloride for injection, the lyophilized powder formulation *[see How Supplied/Storage and Handling (16)].*

2.2 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:

Delay bendamustine hydrochloride for injection administration in the event of Grade 4 hematologic toxicity or clinically significant ≥ 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) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], reinitiate bendamustine hydrochloride for 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^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.

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

2.3 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:

Delay bendamustine hydrochloride for injection 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 ≤ Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], reinitiate bendamustine hydrochloride for 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 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.

2.4 Preparation for Intravenous Administration

Bendamustine hydrochloride for injection is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Bendamustine hydrochloride for injection (25 mg/vial or 100 mg/vial lyophilized powder)

If a closed system transfer device or adapter that contains polycarbonate or ABS is to be used as supplemental protection during preparation[1], only use bendamustine hydrochloride for injection, the lyophilized formulation.

- Each vial of bendamustine hydrochloride for injection is intended for single-dose only.
- Aseptically reconstitute each bendamustine hydrochloride for injection vial as follows:
  - 25 mg bendamustine hydrochloride for injection vial: Add 5 mL of only Sterile Water for Injection, USP.
  - 100 mg bendamustine hydrochloride for injection vial: Add 20 mL of only Sterile Water for Injection, USP.
- Shake well to yield a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. If particulate matter is observed, the reconstituted product should not be used.
- Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) 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 to 0.6 mg/mL. After transferring, thoroughly mix the contents of the infusion bag.
- Visually inspect the filled syringe and the prepared infusion bag to ensure the lack of visible particulate matter prior to administration. The admixture should be a clear and colorless to slightly yellow solution.

Use Sterile Water for Injection, USP, for reconstitution and then 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.

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.

2.5 Admixture Stability

Bendamustine hydrochloride for injection contain no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration.

Bendamustine hydrochloride for injection (25 mg/vial or 100 mg/vial lyophilized powder)

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours stored under refrigerated conditions at 2°C to 8°C (36°F to 46°F) or for **3 hours** when stored at room temperature (15°C to 30°C or 59°F to 86°F) and room light. Administration of reconstituted and diluted bendamustine hydrochloride for injection must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

Bendamustine hydrochloride for injection, USP 25 mg or 100 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

Bendamustine hydrochloride is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine. *[see Warnings and Precautions (5.4)]*

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Bendamustine hydrochloride caused severe myelosuppression (Grade 3 to 4) in 98% of patients in the two NHL studies *[see Adverse Reactions (6.1)]*. 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).

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 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 ≥ 1×10^9/L and the platelet count should be ≥ 75×10^9/L. *[see Dosage and Administration (2.2) and (2.3)]*

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 *[see Adverse Reactions (6.1, 6.2)]*. Patients with myelosuppression following treatment with bendamustine hydrochloride are more susceptible to infections. Advise patients with myelosuppression following bendamustine hydrochloride treatment to contact a physician 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 Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML), including fatal cases, have occurred following treatment with bendamustine, primarily in combination with rituximab or obinutuzumab *[see Adverse Reactions (6.2)].* Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected, withhold bendamustine hydrochloride treatment and perform appropriate diagnostic evaluations. Consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.4 Anaphylaxis and Infusion Reactions

Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials *[see Adverse Reactions (6.1)]*. 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 subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions. Discontinue bendamustine hydrochloride for patients with Grade 4 infusion reactions. Consider discontinuation for Grade 3 infusions reactions as clinically appropriate considering individual benefits, risks, and supportive care.

5.5 Tumor Lysis Syndrome

Tumor lysis syndrome associated with bendamustine hydrochloride treatment has occurred in patients in clinical trials and in postmarketing reports *[see Adverse Reactions (6.1)]*. The onset tends to be within the first treatment cycle of bendamustine hydrochloride and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of bendamustine hydrochloride therapy. However, there may be an increased risk of severe skin toxicity when bendamustine hydrochloride and allopurinol are administered concomitantly *[see Warnings and Precautions (5.6)]*.

5.6 Skin Reactions

Fatal and serious skin reactions have been reported with bendamustine hydrochloride treatment in clinical trials and postmarketing safety reports, including toxic skin reactions [Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)], bullous exanthema, and rash *[see Adverse Reactions (6.1, 6.2)]*. Events occurred when bendamustine hydrochloride was given as a single agent and in combination with other anticancer agents or allopurinol.

Where skin reactions occur, they may be progressive and increase in severity with further treatment. Monitor patients with skin reactions closely. If skin reactions are severe or progressive, withhold or discontinue bendamustine hydrochloride.

5.7 Hepatotoxicity

Fatal and serious cases of liver injury have been reported with bendamustine hydrochloride *[see Adverse Reactions (6.1)]*. Combination therapy, progressive disease or reactivation of hepatitis B were confounding factors in some patients *[see Warnings and Precautions (5.2)]*. Most cases were reported within the first three months of starting therapy. Monitor liver chemistry tests prior to and during bendamustine therapy.

5.8 Other Malignancies

There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with bendamustine hydrochloride, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, bronchial carcinoma, and non-melanoma skin cancer, including basal cell carcinoma and squamous cell carcinoma *[see Adverse Reactions (6.2)]*.

Monitor patients for the development of secondary malignancies. Perform dermatologic evaluations during and after treatment with bendamustine hydrochloride.

5.9 Extravasation Injury

Bendamustine hydrochloride extravasations have been reported in postmarketing resulting in hospitalizations from erythema, marked swelling, and pain *[see Adverse Reactions (6.2)].* Assure good venous access prior to starting bendamustine hydrochloride infusion and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of bendamustine hydrochloride.

5.10 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and the drug’s mechanism of action, bendamustine hydrochloride can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine (that approximated the maximum recommended human dose based on body surface area) to pregnant mice and rats during organogenesis caused adverse developmental outcomes, including an increase in resorptions, skeletal and visceral malformations, and decreased fetal body

weights. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with bendamustine hydrochloride and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with bendamustine hydrochloride and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions have been associated with bendamustine hydrochloride in clinical trials and are discussed in greater detail in other sections of the label.

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.3)]*
- Anaphylaxis and Infusion Reactions *[see Warnings and Precautions (5.4)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.5)]*
- Skin Reactions *[see Warnings and Precautions (5.6)]*
- Hepatotoxicity *[see Warnings and Precautions (5.7)]*
- Other Malignancies *[see Warnings and Precautions (5.8)]*
- Extravasation Injury *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Chronic Lymphocytic Leukemia

The data described below reflect exposure to bendamustine hydrochloride in 153 patients. Bendamustine hydrochloride was studied in an active-controlled, randomized trial. The population was 45 to 77 years of age, 63% male, 100% white, and had treatment naïve CLL. All patients started the study at a dose of 100 mg/m^2 intravenously over 30 minutes on Days 1 and 2 every 28 days.

Adverse reactions were reported according to NCI CTC v.2.0. In the randomized CLL clinical study, non-hematologic adverse reactions (any grade) in the bendamustine hydrochloride group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%).

Other adverse reactions seen frequently in one or more studies included asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis.

Worsening hypertension was reported in 4 patients treated with bendamustine hydrochloride in the randomized CLL clinical study and in none treated with chlorambucil. Three of these 4 adverse reactions were described as a hypertensive crisis and were managed with oral medications and resolved.

The most frequent adverse reactions leading to study withdrawal for patients receiving bendamustine hydrochloride were hypersensitivity (2%) and pyrexia (1%).

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in ≥ 5% of patients in either treatment group in the randomized CLL clinical study.

Table 1: Non- Hematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

	Number (%) of patients			
	Bendamustine Hydrochloride (N=153)		Chlorambucil (N=143)	
Body System/ Adverse Reaction	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Total number of patients with at least 1 adverse reaction	**121 (79)**	**52 (34)**	**96 (67)**	**25 (17)**
Gastrointestinal disorders				
Nausea	31 (20)	1(<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
General disorders and administration site conditions				
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Fatigue	14 (9)	2 (1)	8 (6)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	1 (<1)	0
Immune system disorders				
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	10 (7)	0	12 (8)	0
Infection	9 (6)	3 (2)	1 (<1)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0
Investigations				
Weight decreased	11 (7)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	11 (7)	3 (2)	2 (1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	12 (8)	4 (3)	7 (5)	3 (2)
Pruritus	8 (5)	0	2 (1)	0

The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2. These findings confirm the myelosuppressive effects seen in patients treated with bendamustine hydrochloride. Red blood cell transfusions were administered to 20% of patients receiving bendamustine hydrochloride compared with 6% of patients receiving chlorambucil.

Table 2: Incidence of Hematology Laboratory Abnormalities in Patients Who Received Bendamustine Hydrochloride or Chlorambucil in the Randomized CLL Clinical Study

	Bendamustine Hydrochloride N=150		Chlorambucil N=141	
Laboratory Abnormality	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Hemoglobin Decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets Decreased	116 (77)	16 (11)	110 (78)	14 (10)
Leukocytes Decreased	92 (61)	42 (28)	26 (18)	4 (3)
Lymphocytes Decreased	102 (68)	70 (47)	27 (19)	6 (4)
Neutrophils Decreased	113 (75)	65 (43)	86 (61)	30 (21)

In the randomized CLL trial, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of Grade 3 or 4 were limited to 1% and 3% of patients, respectively. Patients treated with bendamustine hydrochloride may also have changes in their creatinine levels. If abnormalities are detected, monitoring of these parameters should be continued to ensure that further deterioration does not occur.

Non-Hodgkin Lymphoma

The data described below reflect exposure to bendamustine hydrochloride in 176 patients with indolent B-cell NHL treated in two single-arm studies. The population was 31 to 84 years of age, 60% male, and 40% female. The race distribution was 89% White, 7% Black, 3% Hispanic, 1% other, and <1% Asian. These patients received bendamustine hydrochloride at a dose of 120 mg/m^2 intravenously on Days 1 and 2 for up to eight 21-day cycles.

The adverse reactions occurring in at least 5% of the NHL patients, regardless of severity, are shown in Table 3. The most common non-hematologic adverse reactions (≥30%) were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%) and pyrexia (34%). The most common non-hematologic Grade 3 or 4 adverse reactions (≥5%) were fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia and dehydration, each reported in 5% of patients.

Table 3: Non-Hematologic Adverse Reactions Occurring in at Least 5% of NHL Patients Treated with Bendamustine Hydrochloride (N=176)

	Number (%) of patients*	
Body System/ Adverse Reaction	**All Grades**	**Grade 3/4**
Total number of patients with at least 1 adverse reaction	176 (100)	94 (53)
Cardiac disorders		

Tachycardia	13 (7)	0
Gastrointestinal disorders		
Nausea	132 (75)	7 (4)
Vomiting	71 (40)	5 (3)
Diarrhea	65 (37)	6 (3)
Constipation	51 (29)	1 (<1)
Stomatitis	27 (15)	1 (<1)
Abdominal pain	22 (13)	2 (1)
Dyspepsia	20 (11)	0
Gastroesophageal reflux disease	18 (10)	0
Dry mouth	15 (9)	1 (<1)
Abdominal pain upper	8 (5)	0
Abdominal distension	8 (5)	0
General disorders and administration site conditions		
Fatigue	101 (57)	19 (11)
Pyrexia	59 (34)	3 (2)
Chills	24 (14)	0
Edema peripheral	23 (13)	1 (<1)
Asthenia	19 (11)	4 (2)
Chest pain	11 (6)	1 (<1)
Infusion site pain	11 (6)	0
Pain	10 (6)	0
Catheter site pain	8 (5)	0
Infections and infestations		
Herpes zoster	18 (10)	5 (3)
Upper respiratory tract infection	18 (10)	0
Urinary tract infection	17 (10)	4 (2)
Sinusitis	15 (9)	0
Pneumonia	14 (8)	9 (5)
Febrile neutropenia	11 (6)	11 (6)
Oral candidiasis	11 (6)	2 (1)
Nasopharyngitis	11 (6)	0
Investigations		
Weight decreased	31 (18)	3 (2)
Metabolism and nutrition disorders		
Anorexia	40 (23)	3 (2)
Dehydration	24 (14)	8 (5)
Decreased appetite	22 (13)	1 (<1)
Hypokalemia	15 (9)	9 (5)
Musculoskeletal and connective tissue disorders		
Back pain	25 (14)	5 (3)
Arthralgia	11 (6)	0
Pain in extremity	8 (5)	2 (1)
Bone pain	8 (5)	0
Nervous system disorders		
Headache	36 (21)	0
Dizziness	25 (14)	0

Dysgeusia	13 (7)	0
Psychiatric disorders		
Insomnia	23 (13)	0
Anxiety	14 (8)	1(<1)
Depression	10 (6)	0
Respiratory, thoracic and mediastinal disorders		
Cough	38 (22)	1 (<1)
Dyspnea	28 (16)	3 (2)
Pharyngolaryngeal pain	14 (8)	1 (<1)
Wheezing	8 (5)	0
Nasal congestion	8 (5)	0
Skin and subcutaneous tissue disorders		
Rash	28 (16)	1 (<1)
Pruritus	11 (6)	0
Dry skin	9 (5)	0
Night sweats	9 (5)	0
Hyperhidrosis	8 (5)	0
Vascular disorders		
Hypotension	10 (6)	2 (1)

* Patients may have reported more than 1 adverse reaction.
NOTE: Patients counted only once in each adverse reaction category and once in each body system category.

Hematologic toxicities, based on laboratory values and CTC grade, in NHL patients treated in both single arm studies combined are described in Table 4. Clinically important chemistry laboratory values that were new or worsened from baseline and occurred in >1% of patients at Grade 3 or 4, in NHL patients treated in both single arm studies combined were hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).

Table 4: Incidence of Hematology Laboratory Abnormalities in Patients Who Received Bendamustine Hydrochloride in the NHL Studies

Hematology variable	Percent of patients	
	All Grades	Grade 3/4
Lymphocytes Decreased	99	94
Leukocytes Decreased	94	56
Hemoglobin Decreased	88	11
Neutrophils Decreased	86	60
Platelets Decreased	86	25

In both studies, serious adverse reactions, regardless of causality, were reported in 37% of patients receiving bendamustine hydrochloride. The most common serious adverse reactions occurring in ≥5% of patients were febrile neutropenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or postmarketing experience were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome.

Serious drug-related adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumor lysis syndrome and infusion reactions. Adverse reactions occurring less frequently but possibly related to bendamustine hydrochloride treatment were hemolysis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and skin necrosis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of bendamustine hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic systems disorders: Pancytopenia

Cardiovascular disorders: Atrial fibrillation, congestive heart failure (some fatal), myocardial infarction (some fatal), palpitation

General disorders and administration site conditions: Injection site reactions (including phlebitis, pruritus, irritation, pain, swelling), infusion site reactions (including phlebitis, pruritus, irritation, pain, swelling)

Immune system disorders: Anaphylaxis

Infections and infestations: Pneumocystis jiroveci pneumonia, progressive multifocal leukoencephalopathy (PML)

Renal and urinary disorders: Nephrogenic diabetes insipidus (NDI)

Respiratory, thoracic and mediastinal disorders: Pneumonitis

Skin and subcutaneous tissue disorders: Drug reaction with eosinophilia and systemic symptoms (DRESS), non-melanoma skin cancer (NMSC), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Bendamustine Hydrochloride

CYP1A2 Inhibitors

The coadministration of bendamustine hydrochloride with CYP1A2 inhibitors may increase bendamustine plasma concentrations and may result in increased incidence of adverse reactions with bendamustine hydrochloride *[see Clinical Pharmacology (12.3)]*. Consider alternative therapies that are not CYP1A2 inhibitors during treatment with bendamustine hydrochloride.

CYP1A2 Inducers

The coadministration of bendamustine hydrochloride with CYP1A2 inducers may

decrease bendamustine plasma concentrations and may result in decreased efficacy of bendamustine hydrochloride *[see Clinical Pharmacology (12.3)]*. Consider alternative therapies that are not CYP1A2 inducers during treatment with bendamustine hydrochloride.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In animal reproduction studies, intraperitoneal administration of bendamustine to pregnant mice and rats during organogenesis at doses 0.6 to 1.8 times the maximum recommended human dose (MRHD) resulted in embryo-fetal and/or infant mortality, structural abnormalities, and alterations to growth *(see Data)*. There are no available data on bendamustine hydrochloride use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal data

Bendamustine hydrochloride was intraperitoneally administered once to mice from 210 mg/m^2 (approximately 1.8 times the MRHD) during organogenesis and caused an increase in resorptions, skeletal and visceral malformations (exencephaly, cleft palates, accessory rib, and spinal deformities), and decreased fetal body weights. This dose did not appear to be maternally toxic and lower doses were not evaluated. Repeat intraperitoneal administration of bendamustine hydrochloride to mice on gestation days 7 to 11 resulted in an increase in resorptions from 75 mg/m^2 (approximately 0.6 times the MRHD) and an increase in abnormalities from 112.5 mg/m^2 (approximately 0.9 times the MRHD), similar to those seen after a single intraperitoneal administration.

Bendamustine hydrochloride was intraperitoneally administered once to rats from 120 mg/m^2 (approximately the MRHD) on gestation days 4, 7, 9, 11, or 13 and caused embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in external (effect on tail, head, and herniation of external organs [exomphalos]) and internal (hydronephrosis and hydrocephalus) malformations were seen in dosed rats.

8.2 Lactation

Risk Summary

There are no data on the presence of bendamustine hydrochloride or its metabolites in either human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with bendamustine hydrochloride, and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Bendamustine hydrochloride can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiation of treatment with bendamustine hydrochloride.

Contraception

Females

Bendamustine hydrochloride can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)].* Advise female patients of reproductive potential to use effective contraception during treatment with bendamustine hydrochloride and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with bendamustine hydrochloride and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on findings from clinical studies, bendamustine hydrochloride may impair male fertility. Impaired spermatogenesis, azoospermia, and total germinal aplasia have been reported in male patients treated with alkylating agents, especially in combination with other drugs. In some instances spermatogenesis may return in patients in remission, but this may occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacities.

Based on findings from animal studies, bendamustine hydrochloride may impair male fertility due to an increase in morphologically abnormal spermatozoa. The long-term effects of bendamustine hydrochloride on male fertility, including the reversibility of adverse effects, have not been studied *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Safety, pharmacokinetics and efficacy were assessed in a single open-label trial (NCT01088984) in patients aged 1 to 19 years with relapsed or refractory acute leukemia, including 27 patients with acute lymphocytic leukemia (ALL) and 16 patients with acute myeloid leukemia (AML). Bendamustine hydrochloride was administered as an intravenous infusion over 60 minutes on Days 1 and 2 of each 21-day cycle. There was no treatment response (CR+ CRp) in any patient in the Phase 2 portion of the trial at a dose of 120 mg/m^2. However, 2 patients with ALL achieved CR at a dose of 90 mg/m^2 in the Phase 1 portion of the study. The safety profile in these patients was consistent with that seen in adults, and no new safety signals were identified.

The pharmacokinetics of bendamustine in 43 patients, aged 1 to 19 years (median age of 10 years) were within range of values previously observed in adults given the same dose based on body surface area.

8.5 Geriatric Use

No overall differences in safety were observed between patients ≥65 years of age and younger patients. Efficacy was lower in patients 65 and over with CLL receiving bendamustine hydrochloride based upon an overall response rate of 47% for patients 65 and over and 70% for younger patients. Progression free survival was also longer in younger patients with CLL receiving bendamustine hydrochloride (19 months vs. 12 months). No overall differences in efficacy in patients with non-Hodgkin Lymphoma were observed between geriatric patients and younger patients.

8.6 Renal Impairment

Do not use bendamustine hydrochloride in patients with creatinine clearance (CLcr) < 30 mL/min. *[see Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

Do not use bendamustine hydrochloride in patients with AST or ALT 2.5 to 10 × upper limit of normal (ULN) and total bilirubin 1.5 to 3 × ULN, or total bilirubin > 3 × ULN *[see Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

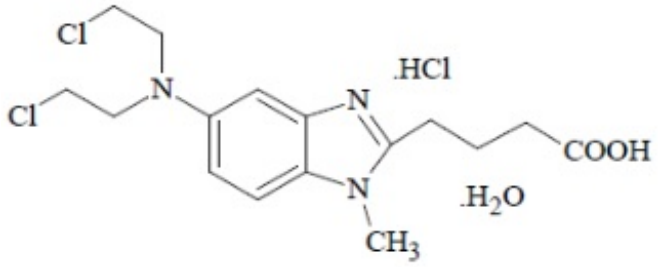
The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

Across all clinical experience, the reported maximum single dose received was 280 mg/m^2. Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients) and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients.

No specific antidote for bendamustine hydrochloride overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

11 DESCRIPTION

Bendamustine hydrochloride, USP is an alkylating agent. The chemical name of bendamustine hydrochloride, USP is 4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid hydrochloride monohydrate. Its molecular formula is $C_{16}H_{21}Cl_2N_3O_2.HCl.H_2O$ and the molecular weight is 412.74. Bendamustine hydrochloride, USP contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:



Bendamustine hydrochloride for injection, USP (25 mg/vial or 100 mg/vial lyophilized powder)

Bendamustine hydrochloride for injection, USP for intravenous use is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single-dose vial. Each 25 mg vial contains 25 mg of bendamustine hydrochloride, USP and 42.5 mg of mannitol, USP. Each 100 mg vial contains 100 mg of bendamustine hydrochloride, USP and 170 mg of mannitol, USP. The pH of the reconstituted solution is 2.5 to 3.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown.

12.2 Pharmacodynamics

Based on the pharmacokinetics/pharmacodynamics analyses of data from adult NHL patients, nausea increased with increasing bendamustine C_{max}.

Cardiac Electrophysiology

The effect of bendamustine on the QTc interval was evaluated in 53 patients with indolent NHL and mantle cell lymphoma on Day 1 of Cycle 1 after administration of rituximab at 375 mg/m^2 intravenous infusion followed by a 30-minute intravenous infusion of bendamustine at 90 mg/m^2/day. No mean changes greater than 20 milliseconds were detected up to one hour post-infusion. The potential for delayed effects on the QT interval after one hour was not evaluated.

12.3 Pharmacokinetics

Absorption

Following a single intravenous dose of bendamustine hydrochloride C_{max} typically occurred at the end of infusion. The dose proportionality of bendamustine has not been studied.

Distribution

The protein binding of bendamustine ranged from 94 to 96% and was concentration independent from 1 to 50 mcg/mL. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 mcg/mL.

The mean steady-state volume of distribution (V_{ss}) of bendamustine was approximately 20 to 25 L.

Elimination

After a single intravenous dose of 120 mg/m^2 of bendamustine over 1 hour, the intermediate half-life ($t_{½}$) of the parent compound is approximately 40 minutes. The mean terminal elimination t½ of two active metabolites, γ-hydroxybendamustine (M3) and N desmethylbendamustine (M4) are approximately 3 hours and 30 minutes, respectively. Bendamustine clearance in humans is approximately 700 mL/min.

Metabolism

Bendamustine is extensively metabolized via hydrolytic, oxidative, and conjugative pathways. Bendamustine is primarily metabolized via hydrolysis to monohydroxy (HP1) and dihydroxy-bendamustine (HP2) metabolites with low cytotoxic activity *in vitro*. Two active minor metabolites, M3 and M4, are primarily formed via CYP1A2 *in vitro*. M3 and M4 concentrations in plasma are 1/10th and 1/100th that of the parent compound, respectively.

Excretion

Following intravenous infusion of radiolabeled bendamustine hydrochloride in cancer patients, approximately 76% of the dose was recovered. Approximately 50% of the dose was recovered in the urine (3.3% unchanged) and approximately 25% of the dose was recovered in the feces. Less than 1% of the dose was recovered in the urine as M3 and M4, and less than 5% of the dose was recovered in the urine as HP2.

Specific Populations

No clinically meaningful effects on the pharmacokinetics of bendamustine were observed based on age (31 to 84 years), sex, mild to moderate renal impairment (CLcr ≥ 30 mL/min), or hepatic impairment with total bilirubin 1.5 < ULN and AST or ALT < 2.5 × ULN. The effects of severe renal impairment (CLcr < 30 mL/min), or hepatic impairment with total bilirubin 1.5 to 3 × ULN and AST or ALT 2.5 to 10 × ULN or total bilirubin > 3 × ULN on the pharmacokinetics of bendamustine is unknown.

Race/Ethnicity

Exposures in Japanese subjects (n=6) were 40% higher than that in non-Japanese subjects receiving the same dose. The clinical importance of this difference on the safety and efficacy of bendamustine hydrochloride in Japanese subjects has not been established.

Drug Interaction Studies

In Vitro Studies

Effect of Bendamustine on CYP Substrates

Bendamustine did not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5.

Effect of Transporters on Bendamustine Hydrochloride

Bendamustine is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bendamustine was carcinogenic in mice. After intraperitoneal injections at 37.5 mg/m^2/day (the lowest dose tested, approximately 0.3 times the maximum recommended human dose [MRHD])) and 75 mg/m^2/day (approximately 0.6 times the MRHD) for 4 days, peritoneal sarcomas in female AB/Jena mice were produced. Oral administration at 187.5 mg/m^2/day (the only dose tested, approximately 1.6 times the MRHD) for 4 days induced mammary carcinomas and pulmonary adenomas.

Bendamustine is a mutagen and clastogen. In a bacterial reverse mutation assay (Ames assay), bendamustine was shown to increase revertant frequency in the absence and presence of metabolic activation. Bendamustine was clastogenic in human lymphocytes *in vitro*, and in rat bone marrow cells *in vivo* (increase in micronucleated polychromatic erythrocytes) from 37.5 mg/m^2 (the lowest dose tested, approximately 0.3 times the MRHD).

Bendamustine induced morphologic abnormalities in spermatozoa in mice. Following tail vein injection of bendamustine at 120 mg/m^2 or a saline control on days 1 and 2 for a total of 3 weeks, the number of spermatozoa with morphologic abnormalities was 16% higher in the bendamustine-treated group as compared to the saline control group.

14 CLINICAL STUDIES

14.1 Chronic Lymphocytic Leukemia (CLL)

The safety and efficacy of bendamustine hydrochloride were evaluated in an open-label, randomized, controlled multicenter trial comparing bendamustine hydrochloride to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I to IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

The patient populations in the bendamustine hydrochloride and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean 65.7×10^9/L vs. 65.1×10^9/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either bendamustine hydrochloride at 100 mg/m^2, administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL.

The results of this open-label randomized study demonstrated a higher rate of overall response and a longer progression-free survival for bendamustine hydrochloride compared to chlorambucil (see Table 5). Survival data are not mature.

Table 5: Efficacy Data for CLL

	Bendamustine Hydrochloride (N=153)	**Chlorambucil (N=148)**	**p-value**
Response Rate n (%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95% CI)	(51.0, 66.6)	(18.6, 32.7)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)**	4 (3)	0	
Partial response (PR)†	73 (48)	37 (25)	
Progression-Free Survival††			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		<0.0001

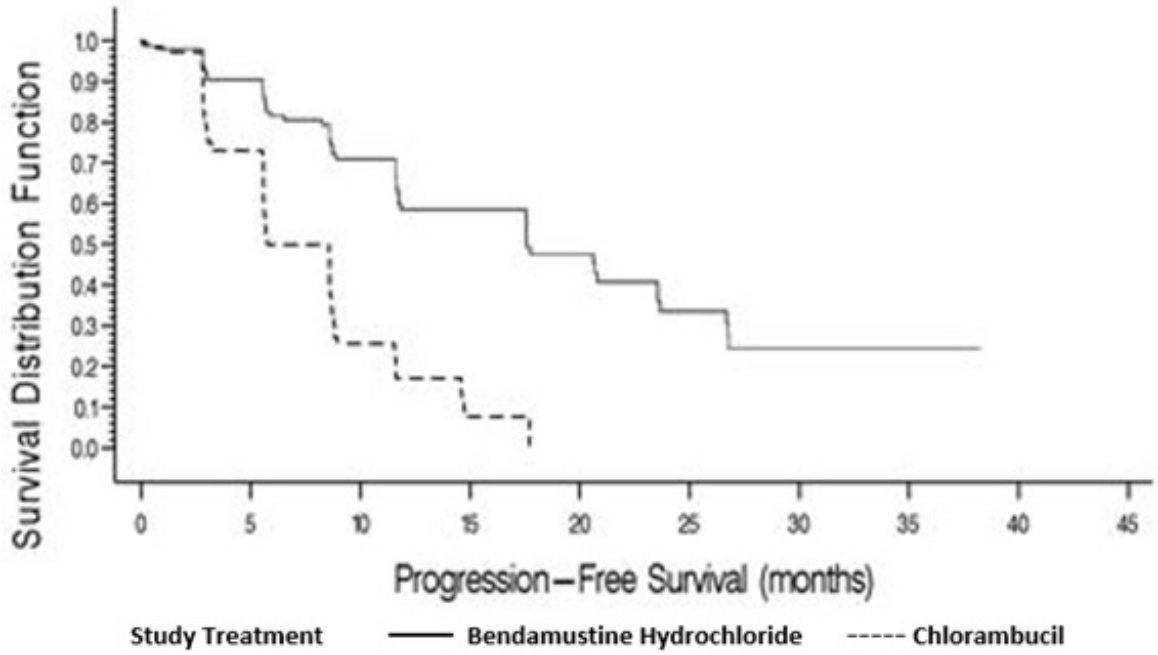
CI = confidence interval

* CR was defined as peripheral lymphocyte count ≤ 4.0×10^9/L, neutrophils ≥ 1.5×10^9/L, platelets >100×10^9/L, hemoglobin > 110 g/L, without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms. The

clinical and laboratory criteria were required to be maintained for a period of at least 56 days.
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.
† PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, hemoglobin >110 g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.
†† PFS was defined as time from randomization to progression or death from any cause.

Kaplan-Meier estimates of progression-free survival comparing bendamustine hydrochloride with chlorambucil are shown in Figure 1.

Figure 1. Progression-Free Survival



14.2 Non-Hodgkin Lymphoma (NHL)

The efficacy of bendamustine hydrochloride was evaluated in a single arm study of 100 patients with indolent B-cell NHL that had progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received bendamustine hydrochloride intravenously at a dose of 120 mg/m^2, on Days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles.

The median age was 60 years, 65% were male, and 95% had a baseline WHO performance status of 0 or 1. Major tumor subtypes were follicular lymphoma (62%), diffuse small lymphocytic lymphoma (21%), and marginal zone lymphoma (16%). Ninety-nine percent of patients had received previous chemotherapy, 91% of patients had received previous alkylator therapy, and 97% of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or

combination therapy) of rituximab.

Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in Table 6.

Table 6: Efficacy Data for NHL*

	Bendamustine Hydrochloride (N=100)
Response Rate (%)	
Overall response rate (CR+CRu+PR)	74
(95% CI)	(64.3, 82.3)
Complete response (CR)	13
Complete response unconfirmed (CRu)	4
Partial response (PR)	57
Duration of Response (DR)	
Median, months (95% CI)	9.2 months (7.1, 10.8)

CI = confidence interval
*IRC assessment was based on modified International Working Group response criteria (IWG-RC). Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm.

15 REFERENCES

1. OSHA Hazardous Drugs.
OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

Safe Handling and Disposal

Bendamustine hydrochloride for injection, USP is a hazardous drug. Follow applicable special handling and disposal procedures1. Care should be exercised in the handling and preparation of solutions prepared from bendamustine hydrochloride for injection, USP. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If gloves come in contact with bendamustine hydrochloride for injection, USP prior to dilution, remove gloves and follow disposal procedures[1]. If a solution of bendamustine hydrochloride for injection, USP contacts the skin, wash the skin immediately and thoroughly with soap and water. If bendamustine hydrochloride for injection, USP contacts the mucous membranes, flush thoroughly with water.

How Supplied

Bendamustine hydrochloride for injection, USP is supplied in individual cartons as follows:

- NDC 55150-391-01: 25 mg white to off-white lyophilized powder in a 26 mL amber single-dose vial
- NDC 55150-392-01: 100 mg white to off-white lyophilized powder in a 60 mL amber single-dose vial

Storage

Bendamustine hydrochloride for injection, USP may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) [see USP Controlled Room Temperature]. Retain in original package until time of use to protect from light.

The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Allergic (Hypersensitivity) Reactions

Inform patients of the possibility of mild or serious allergic reactions and to immediately report rash, facial swelling, or difficulty breathing during or soon after infusion [*see Warnings and Precautions (5.4)]*.

Myelosuppression

Inform patients of the likelihood that bendamustine hydrochloride will cause a decrease in white blood cells, platelets, and red blood cells, and the need for frequent monitoring of blood counts. Advise patients to report shortness of breath, significant fatigue, bleeding, fever, or other signs of infection *[see Warnings and Precautions (5.1)]*.

Progressive Multifocal Leukoencephalopathy (PML)

Inform patients to immediately contact their healthcare provider if they experience confusion, memory loss, trouble thinking, difficulty talking or walking, vision loss or other neurological or cognitive symptoms *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately contact their health care provider if signs of liver failure occur, including jaundice, anorexia, bleeding or bruising *[see Warnings and Precautions (5.7)]*.

Fatigue

Advise patients that bendamustine hydrochloride may cause tiredness and to avoid driving any vehicle or operating any dangerous tools or machinery if they experience this side effect *[see Adverse Reactions (6.1)]*.

Nausea and Vomiting

Advise patients that bendamustine hydrochloride may cause nausea and/or vomiting. Patients should report nausea and vomiting so that symptomatic treatment may be provided *[see Adverse Reactions (6.1)]*.

Diarrhea

Advise patients that bendamustine hydrochloride may cause diarrhea. Patients should report diarrhea to the physician so that symptomatic treatment may be provided *[see Adverse Reactions (6.1)]*.

Rash

Advise patients that a rash or itching may occur during treatment with bendamustine hydrochloride. Advise patients to immediately report severe or worsening rash or itching *[see Warnings and Precautions (5.6)]*.

Non-Melanoma Skin Cancer (NMSC)

Advise patients to undergo regular skin cancer screenings, and to report any suspicious skin changes to their healthcare provider *[see Warnings and Precautions (5.8)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1, 8.3), and Nonclinical Toxicology (13.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with bendamustine hydrochloride and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with bendamustine hydrochloride and for 3 months after the last dose *[see Use in Specific Populations (8.3), and Nonclinical Toxicology (13.1)]*.

Lactation

Advise females not to breastfeed during treatment with bendamustine hydrochloride and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

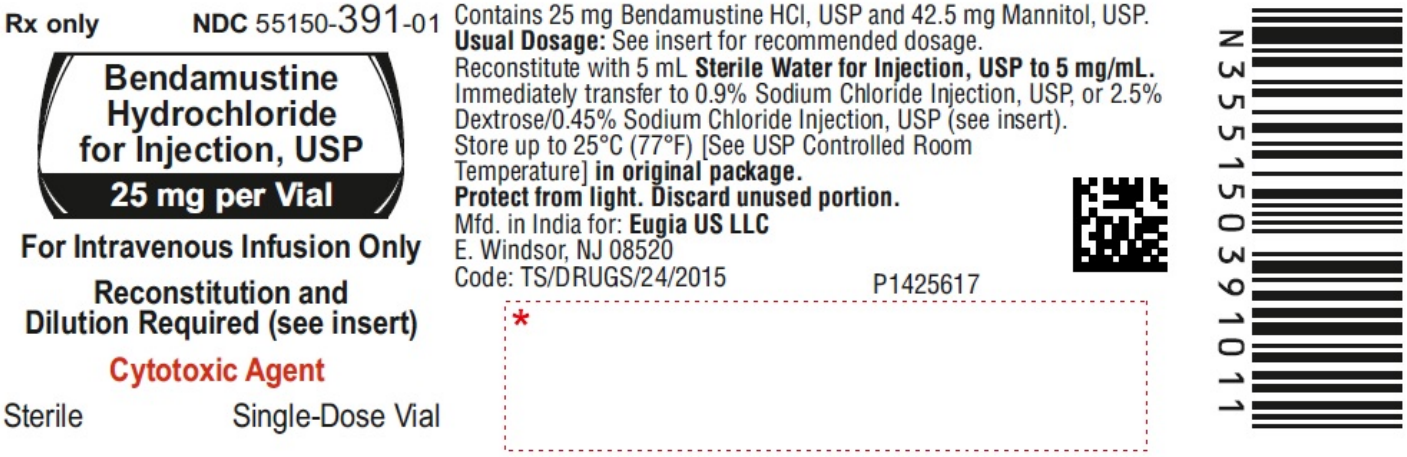
Advise males of reproductive potential that bendamustine hydrochloride may impair fertility *[see Use in Specific Populations (8.3)]*.

Distributed By:
Eugia US LLC
279 Princeton-Hightstown Rd.
E. Windsor, NJ 08520

Manufactured by:
Eugia Pharma Specialities Limited
Hyderabad – 500032
India

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL-25 mg per vial - Container Label

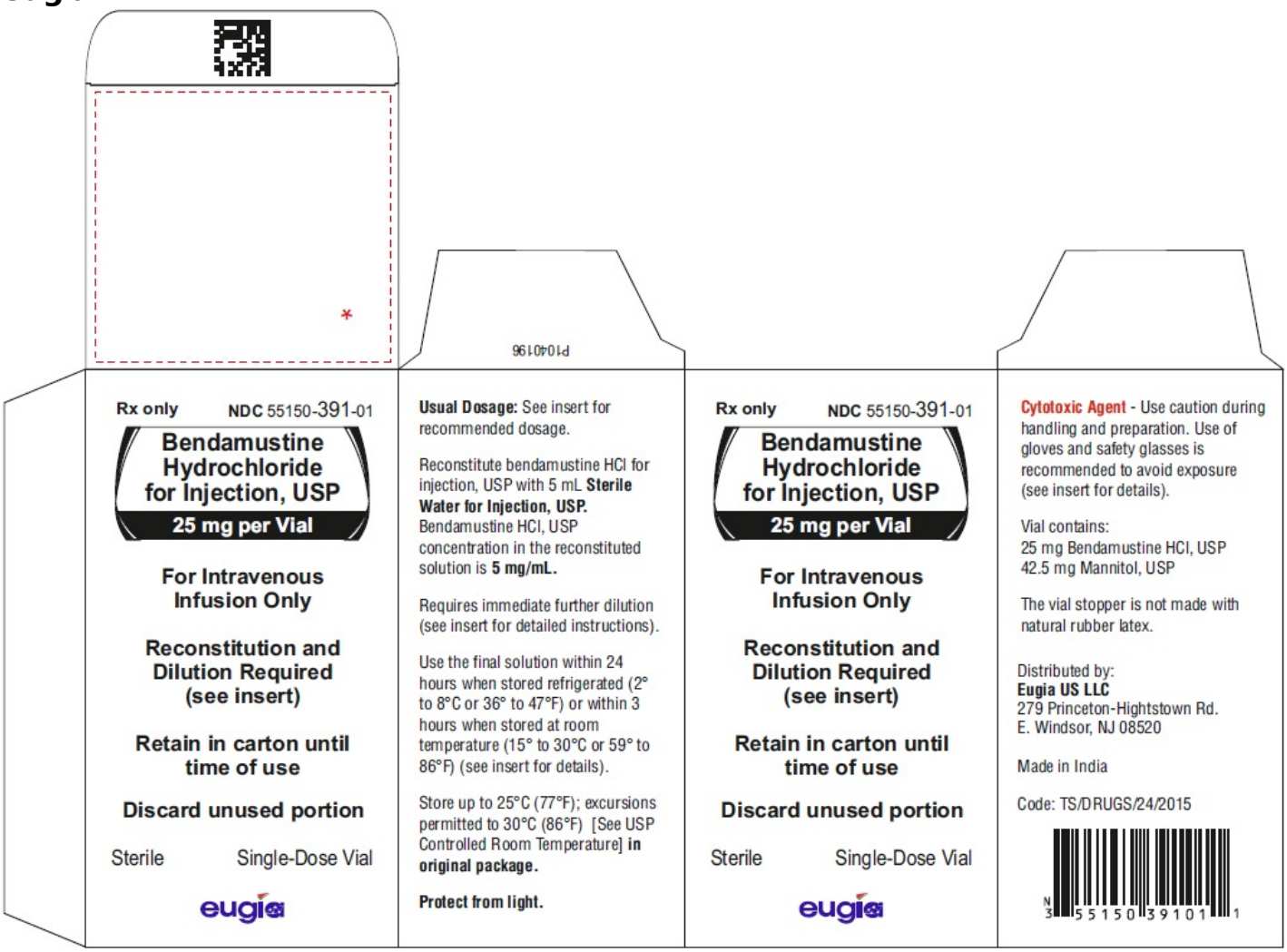
Rx only **NDC** 55150-391-01
Bendamustine HCl
for Injection, USP
25 mg per Vial
For Intravenous Infusion Only
Reconstitution and
Dilution Required (see insert)
Cytotoxic Agent
Sterile Single-Dose Vial



PACKAGE LABEL-PRINCIPAL DISPLAY PANEL-25 mg per vial - Container-Carton (1 Vial)

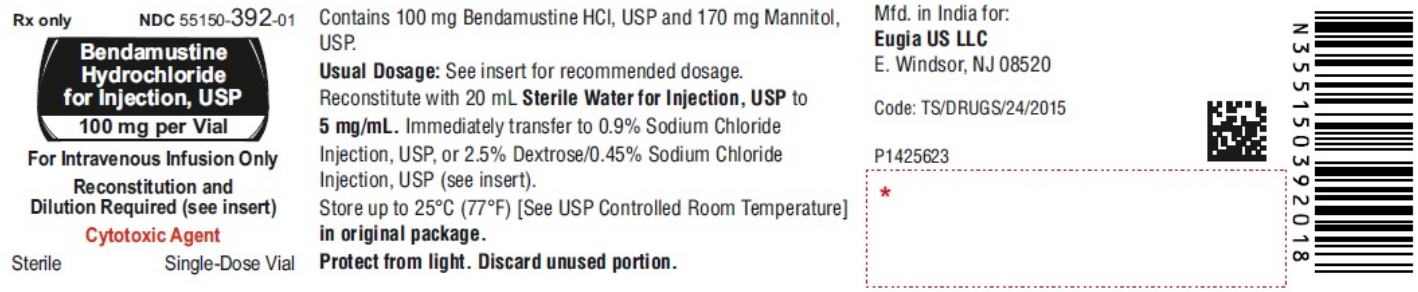
Rx only **NDC** 55150-391-01
Bendamustine
Hydrochloride
for Injection, USP
25 mg per Vial
For Intravenous
Infusion Only
Reconstitution and
Dilution Required
(see insert)
Retain in carton until
time of use
Discard unused portion

Sterile Single-Dose Vial
eugia



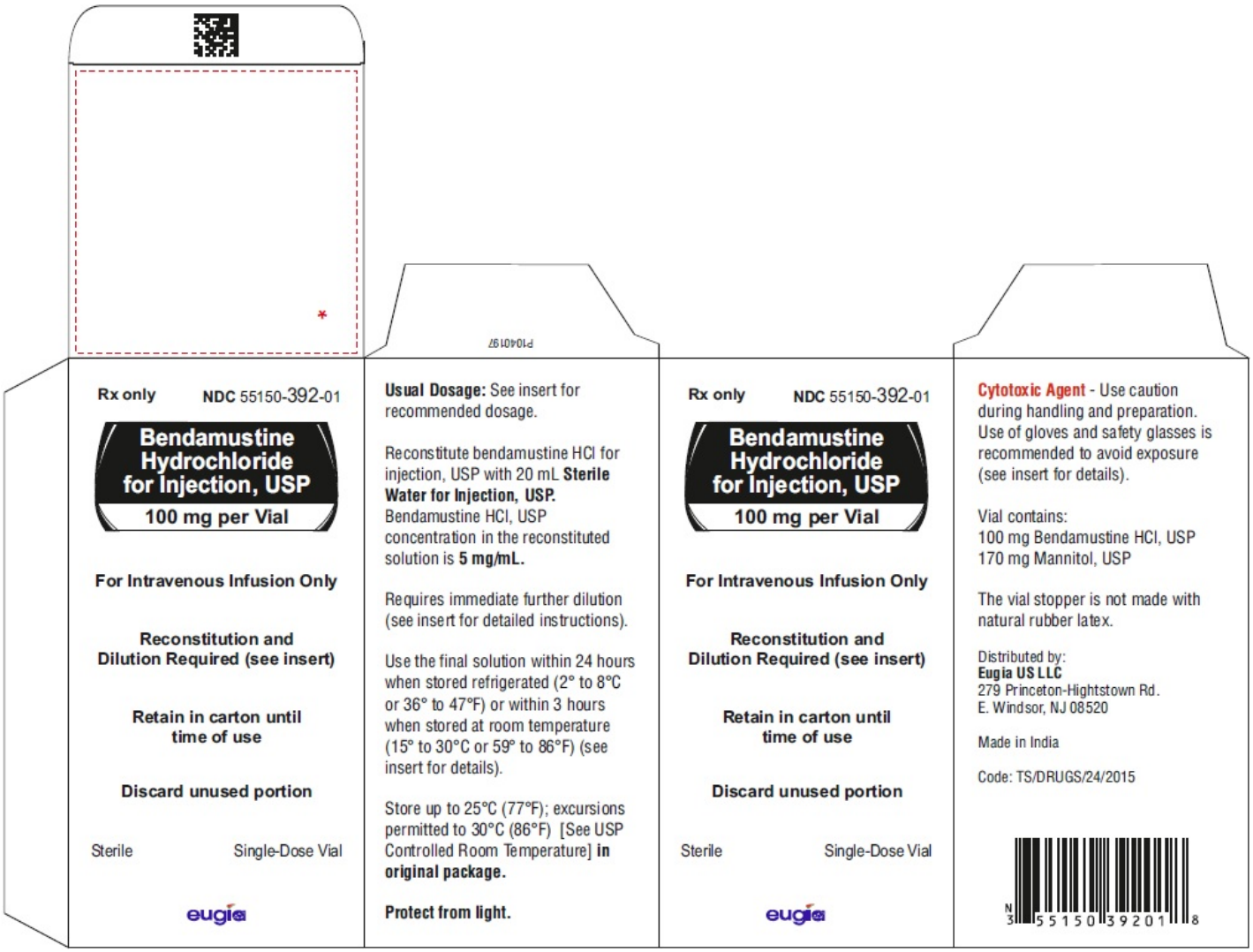
PACKAGE LABEL-PRINCIPAL DISPLAY PANEL-100 mg per vial - Container Label

Rx only **NDC** 55150-392-01
Bendamustine HCl
for Injection, USP
100 mg per Vial
For Intravenous Infusion Only
Reconstitution and
Dilution Required (see insert)
Cytotoxic Agent
Sterile Single-Dose Vial



PACKAGE LABEL-PRINCIPAL DISPLAY PANEL-100 mg per vial - Container-Carton (1 Vial)

Rx only **NDC** 55150-392-01
Bendamustine
Hydrochloride
for Injection, USP
100 mg per Vial
For Intravenous Infusion Only
Reconstitution and
Dilution Required (see insert)
Retain in carton until
time of use
Discard unused portion
Sterile Single-Dose Vial
eugia



BENDAMUSTINE HYDROCHLORIDE

bendamustine hydrochloride injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55150-391
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BENDAMUSTINE HYDROCHLORIDE (UNII: 981Y8SX18M) (BENDAMUSTINE - UNII:9266D9P3PQ)	BENDAMUSTINE HYDROCHLORIDE	25 mg in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55150-391-01	1 in 1 CARTON	06/05/2023	
1		5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA214739	06/05/2023	

BENDAMUSTINE HYDROCHLORIDE

bendamustine hydrochloride injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55150-392
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BENDAMUSTINE HYDROCHLORIDE (UNII: 981Y8SX18M) (BENDAMUSTINE - UNII:9266D9P3PQ)	BENDAMUSTINE HYDROCHLORIDE	100 mg in 20 mL

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55150-392-01	1 in 1 CARTON	06/05/2023	
1		20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA214739	06/05/2023	

Labeler - Eugia US LLC (968961354)

Establishment

Name	Address	ID/FEI	Business Operations
EUGIA Pharma Specialities Limited		872201704	ANALYSIS(55150-391, 55150-392) , MANUFACTURE(55150-391, 55150-392) , PACK(55150-391, 55150-392)

Revised: 7/2023 Eugia US LLC