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

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

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

Warnings and Precautions, Infections (5.2)	11/2015
Warnings and Precautions, Skin Reactions (5.5)	10/2016
Warnings and Precautions, Hepatotoxicity (5.6)	10/2016

----------INDICATIONS AND USAGE----------

TREANDA 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----------

TREANDA is available in two formulations, a solution (TREANDA Injection) and a lyophilized powder (TREANDA for Injection). (2.1)

Do not use TREANDA injection with devices that contain polycarbonate or acrylonitrile-butadiene-styrene (ABS), including most Closed System Transfer Devices (CSTDs). (2.1, 2.4)

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)
- 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. (2.2)
- 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. (2.2)
- Dose re-escalation may be considered. (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)
- 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. (2.3)
- 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)

General Dosing Considerations:

- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. (2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: solution-45 mg/0.5 mL or 180 mg/2 mL in a single-dose vial. (3)
For Injection: 25 mg or 100 mg lyophilized powder in a single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------

TREANDA is contraindicated in patients with a history of a hypersensitivity reaction to bendamustine. Reactions have included anaphylaxis and anaphylactoid reactions. (5.3)

----------WARNINGS AND PRECAUTIONS----------

- Myelosuppression: Delay or reduce dose. Restart treatment based on ANC and platelet count recovery. (2.2) 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 and anaphylactic reactions have occurred; monitor clinically and discontinue TREANDA. 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 TREANDA. (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. (6.1)
- Most common hematologic abnormalities for both indications (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. (6.1)

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: 10/2016

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)

TREANDA® 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)

TREANDA 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 TREANDA Formulation to Administer

TREANDA is available in two formulations, a solution (TREANDA Injection) and a lyophilized powder (TREANDA for Injection).

Do not use TREANDA Injection if you intend to use closed system transfer devices (CSTDs), adapters and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS) prior to dilution in the infusion bag *[see Dosage and Administration (2.4)]*.

If using a syringe to withdraw and transfer TREANDA Injection from the vial into the infusion bag, only use a polypropylene syringe with a metal needle and polypropylene hub to withdraw and transfer TREANDA Injection into the infusion bag. Polypropylene syringes are translucent in appearance.

TREANDA Injection and the reconstituted TREANDA 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.**

TREANDA Injection must be withdrawn and transferred for dilution in a biosafety cabinet (BSC) or containment isolator using a polypropylene syringe with a metal needle and a polypropylene hub.

If a CSTD or adapter that contains polycarbonate or ABS is used as supplemental protection prior to dilution[1], only use TREANDA for Injection, the lyophilized powder formulation *[see How Supplied/Storage and Handling (16.1)]*.

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:

TREANDA administration should be delayed in the event of 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], TREANDA 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.

2.3 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:

TREANDA 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], TREANDA 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.

2.4 Preparation for Intravenous Administration

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

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution)

TREANDA Injection must be diluted in a biosafety cabinet (BSC) or containment isolator.

- **When preparing and transferring the concentrated TREANDA Injection solution into the infusion bag, do not use devices that contain polycarbonate or ABS. However, after dilution of TREANDA Injection into the infusion bag, devices that contain polycarbonate or ABS, including infusion sets, may be used.**

  TREANDA Injection contains N,N-dimethylacetamide (DMA), which is incompatible with devices that contain polycarbonate or ABS. Devices, including CSTDs, adapters, and syringes that contain polycarbonate or ABS have been shown to dissolve when they come in contact with DMA which is present in the product. This incompatibility leads to device failure (e.g., leaking, breaking, or operational failure of CSTD components), possible product contamination, and potential serious adverse health consequences to the practitioner, including skin reactions; or to the patient, including but not limited to, the risk of small blood vessel blockage if they receive product contaminated with dissolved ABS or polycarbonate. Devices that are compatible for use in dilution of TREANDA Injection are available.

- **If using a syringe to withdraw and transfer TREANDA Injection from the vial into the infusion bag, only use a polypropylene syringe with a metal needle and a polypropylene hub to withdraw and transfer TREANDA Injection into the infusion bag.**

- Each vial of TREANDA Injection is intended for single dose only.

- Aseptically withdraw the volume needed for the required dose from the 90 mg/mL solution using a polypropylene syringe with a metal needle and a polypropylene hub.

- Immediately transfer the solution 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 dilution of TREANDA Injection into the infusion bag, devices that contain polycarbonate or ABS, including infusion sets, may be used.**

- 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 colorless to 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.

TREANDA 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 TREANDA for Injection, the lyophilized formulation.

- Each vial of TREANDA for Injection is intended for single dose only.

- Aseptically reconstitute each TREANDA for Injection vial as follows:
  - 25 mg TREANDA for Injection vial: Add 5 mL of only Sterile Water for Injection, USP.
  - 100 mg TREANDA 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 – 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.

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.

2.5 Admixture Stability

TREANDA Injection and TREANDA for Injection contain no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration.

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution)

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 when stored under refrigerated conditions at 2-8°C (36-46°F) or for

2 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted TREANDA Injection must be completed within this period.

TREANDA 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 when stored under refrigerated conditions at 2-8°C (36-46°F) or for

3 hours when stored at room temperature (15-30°C or 59-86°F) and room light**.** Administration of reconstituted and diluted TREANDA for Injection must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

- TREANDA Injection: 45 mg/0.5 mL or 180 mg/2 mL in a single-dose vial.

- TREANDA for Injection: 25 mg or 100 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

TREANDA is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine. *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

TREANDA 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 (2.2) 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. Patients with myelosuppression following treatment with TREANDA are more susceptible to infections. Advise patients with myelosuppression following TREANDA treatment to contact a physician if they have symptoms or signs of infection.

Patients treated with TREANDA 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 TREANDA 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 subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions. Discontinue TREANDA for patients with Grade 4 infusion reactions. Consider discontinuation for Grade 3 infusions reactions as clinically appropriate considering individual benefits, risks, and supportive care.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome associated with TREANDA treatment has occurred in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of TREANDA 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 TREANDA therapy. However, there may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly *[see Warnings and Precautions (5.5)]*.

5.5 Skin Reactions

Fatal and serious skin reactions have been reported with TREANDA 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. Events occurred when TREANDA 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 TREANDA.

5.6 Hepatotoxicity

Fatal and serious cases of liver injury have been reported with TREANDA. 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.

5.7 Other Malignancies

There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with TREANDA, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma.

5.8 Extravasation Injury

TREANDA extravasations have been reported in post marketing resulting in hospitalizations from erythema, marked swelling, and pain. Assure good venous access prior to starting TREANDA infusion and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of TREANDA.

5.9 Embryo-fetal Toxicity

TREANDA can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine in mice and rats administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights. *[see Use in Specific Populations (8.1)]*

6 ADVERSE REACTIONS

The following serious adverse reactions have been associated with TREANDA 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)]*
- Anaphylaxis and Infusion Reactions *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*
- Skin Reactions *[see Warnings and Precautions (5.5)]*
- Hepatotoxicity *[see Warnings and Precautions (5.6)]*
- Other Malignancies *[see Warnings and Precautions (5.7)]*
- Extravasation Injury *[see Warnings and Precautions (5.8)]*

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 TREANDA in 153 patients with CLL studied in an active-controlled, randomized trial. The population was 45-77 years of age, 63% male, 100% white, and were treatment naïve. 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. Non-hematologic adverse reactions (any grade) in the TREANDA 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 TREANDA in the CLL trial 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 TREANDA 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			
	TREANDA (N=153)		Chlorambucil (N=143)	
System organ class **Preferred term**	**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	12 (8)	4 (3)	7 (5)	3 (2)
Rash	8 (5)	0	2 (1)	0
Pruritus				

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 TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

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

	TREANDA 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 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 TREANDA 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 TREANDA in 176 patients with indolent B-cell NHL treated in two single-arm studies. The population was 31-84 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 TREANDA 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 TREANDA by System Organ Class and Preferred Term (N=176)

System organ class Preferred term	Number (%) of patients*	
	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 preferred term category and once in each system organ class 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 TREANDA 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 TREANDA. 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 *[see Warnings and Precautions (5)]*. Adverse reactions occurring less frequently but possibly related to TREANDA 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 TREANDA. 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

Respiratory, thoracic and mediastinal disorders: Pneumonitis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, Toxic epidermal necrolysis, DRESS (Drug reaction with eosinophilia and systemic symptoms). *[see Warnings and Precautions (5.5)]*

7 DRUG INTERACTIONS

No formal clinical assessments of pharmacokinetic drug-drug interactions between TREANDA and other drugs have been conducted.

Bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to

increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

The role of active transport systems in bendamustine distribution has not been fully evaluated. *In vitro* data suggest that P-glycoprotein, breast cancer resistance protein (BCRP), and/or other efflux transporters may have a role in bendamustine transport.

Based on *in vitro* data, bendamustine is not likely to inhibit metabolism via human CYP isoenzymes CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5, or to induce metabolism of substrates of cytochrome P450 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.9)]*

Risk Summary

TREANDA can cause fetal harm when administered to a pregnant woman. Bendamustine caused malformations in animals, when a single dose was administered to pregnant animals. Advise women to avoid becoming pregnant while receiving TREANDA and for 3 months after therapy has stopped. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to a fetus. Advise men receiving TREANDA to use reliable contraception for the same time period.

Animal data

Single intraperitoneal doses of bendamustine from 210 mg/m^2 (70 mg/kg) in mice administered during organogenesis 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 dosing in mice on gestation days 7-11 resulted in an increase in resorptions from 75 mg/m^2 (25 mg/kg) and an increase in abnormalities from 112.5 mg/m^2 (37.5 mg/kg) similar to those seen after a single intraperitoneal administration. Single intraperitoneal doses of bendamustine from 120 mg/m^2 (20 mg/kg) in rats administered on gestation days 4, 7, 9, 11, or 13 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. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8.2 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for bendamustine in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The effectiveness of TREANDA in pediatric patients has not been established. TREANDA was evaluated in a single Phase 1/2 trial in pediatric patients with leukemia. The safety profile for TREANDA in pediatric patients was consistent with that seen in adults, and no new safety signals were identified.

The trial included pediatric patients from 1-19 years of age with relapsed or refractory acute leukemia, including 27 patients with acute lymphocytic leukemia (ALL) and 16 patients with acute myeloid leukemia (AML). TREANDA was administered as an intravenous infusion over 60 minutes on Days 1 and 2 of each 21-day cycle. Doses of 90 and 120 mg/m^2 were evaluated. The Phase 1 portion of the study determined that the recommended Phase 2 dose of TREANDA in pediatric patients was 120 mg/m^2.

A total of 32 patients entered the Phase 2 portion of the study at the recommended dose and were evaluated for response. There was no treatment response (CR+ CRp) in any patient at this dose. However, there were 2 patients with ALL who achieved a CR at a dose of 90 mg/m^2 in the Phase 1 portion of the study.

In the above-mentioned pediatric trial, the pharmacokinetics of TREANDA at 90 and 120 mg/m^2 doses were evaluated in 5 and 38 patients, respectively, aged 1 to 19 years (median age of 10 years).

The geometric mean body surface adjusted clearance of bendamustine was 14.2 L/h/m^2. The exposures (AUC_{0-24} and C_{max}) to bendamustine in pediatric patients following a 120 mg/m^2 intravenous infusion over 60 minutes were similar to those in adult patients following the same 120 mg/m^2 dose.

8.5 Geriatric Use

In CLL and NHL studies, there were no clinically significant differences in the adverse reaction profile between geriatric (≥ 65 years of age) and younger patients.

Chronic Lymphocytic Leukemia

In the randomized CLL clinical study, 153 patients received TREANDA. The overall response rate for patients younger than 65 years of age was 70% (n=82) for TREANDA and 30% (n=69) for chlorambucil. The overall response rate for patients 65 years or older was 47% (n=71) for TREANDA and 22% (n=79) for chlorambucil. In patients younger than 65 years of age, the median progression-free survival was 19 months in the TREANDA group and 8 months in the chlorambucil group. In patients 65 years or older, the median progression-free survival was 12 months in the TREANDA group and 8 months in the chlorambucil group.

Non-Hodgkin Lymphoma

Efficacy (Overall Response Rate and Duration of Response) was similar in patients < 65 years of age and patients ≥ 65 years. Irrespective of age, all of the 176 patients experienced at least one adverse reaction.

8.6 Renal Impairment

No formal studies assessing the impact of renal impairment on the pharmacokinetics of bendamustine have been conducted. TREANDA should be used with caution in patients with mild or moderate renal impairment. TREANDA should not be used in patients with CrCL < 40 mL/min. *[see Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

No formal studies assessing the impact of hepatic impairment on the pharmacokinetics of bendamustine have been conducted. TREANDA should be used with caution in patients with mild hepatic impairment. TREANDA should not be used in patients with moderate (AST or ALT 2.5-10 X ULN and total bilirubin 1.5-3 X ULN) or severe (total bilirubin > 3 X ULN) hepatic impairment. *[see Clinical Pharmacology (12.3)]*

8.8 Effect of Gender

No clinically significant differences between genders were seen in the overall incidences of adverse reactions in either CLL or NHL studies.

Chronic Lymphocytic Leukemia

In the randomized CLL clinical study, the overall response rate (ORR) for men (n=97) and women (n=56) in the TREANDA group was 60% and 57%, respectively. The ORR for men (n=90) and women (n=58) in the chlorambucil group was 24% and 28%, respectively. In this study, the median progression-free survival for men was 19 months in the TREANDA treatment group and 6 months in the chlorambucil treatment group. For women, the median progression-free survival was 13 months in the TREANDA treatment group and 8 months in the chlorambucil treatment group.

Non-Hodgkin Lymphoma

The pharmacokinetics of bendamustine were similar in male and female patients with indolent NHL. No clinically-relevant differences between genders were seen in efficacy (ORR and DR).

10 OVERDOSAGE

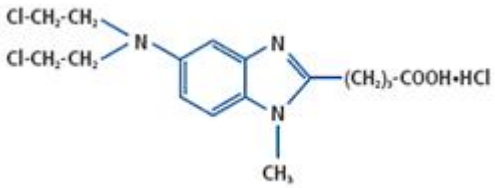
The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

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 TREANDA overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

11 DESCRIPTION

Bendamustine hydrochloride is an alkylating agent. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$, and the molecular weight is 394.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:



TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution)

TREANDA (bendamustine HCl) Injection is intended for intravenous infusion only after dilution with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. It is supplied as a sterile clear colorless to yellow solution in a single-dose vial at the concentration of 90 mg/mL of bendamustine HCl. Each 0.5 mL vial contains 45 mg of bendamustine hydrochloride, 162 mg of Propylene Glycol, USP and 293 mg of N,N-Dimethylacetamide, EP. Each 2 mL vial contains 180 mg of bendamustine hydrochloride, 648 mg of Propylene Glycol, USP and 1172 mg of N,N-Dimethylacetamide, EP. An overfill of 0.2 mL is included in each vial.

TREANDA for Injection (25 mg/vial or 100 mg/vial lyophilized powder)

TREANDA (bendamustine HCl) for Injection is intended for intravenous infusion only after reconstitution with Sterile Water for Injection, USP, and after further dilution with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. It 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 and 42.5 mg of mannitol, USP. Each 100-mg vial contains 100 mg of bendamustine hydrochloride and 170 mg of mannitol, USP. The pH of the reconstituted solution is 2.5 - 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 IV dose of bendamustine hydrochloride C_{max} typically occurred at the end of infusion. The dose proportionality of bendamustine has not been studied.

Distribution

In vitro, the binding of bendamustine to human serum plasma proteins ranged from 94-96% and was concentration independent from 1-50 μg/mL. Data suggest that bendamustine is not likely to displace or to be displaced by highly protein-bound drugs. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 μg/mL indicating that bendamustine distributes freely in human red blood cells.

In a mass balance study, plasma radioactivity levels were sustained for a greater period of time than plasma concentrations of bendamustine, γ hydroxybendamustine (M3), and N desmethylbendamustine (M4). This suggests that there are bendamustine derived materials (detected via the radiolabel), that are rapidly cleared and have a longer half-life than bendamustine and its active metabolites.

The mean steady-state volume of distribution (V_{ss}) of bendamustine was approximately 20-25 L. Steady-state volume of distribution for total radioactivity was approximately 50 L, indicating that neither bendamustine nor total radioactivity are extensively distributed into the tissues.

Metabolism

In vitro data indicate that bendamustine is primarily metabolized via hydrolysis to monohydroxy (HP1) and dihydroxy-bendamustine (HP2) metabolites with low cytotoxic activity. Two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are $1/10^{th}$ and $1/100^{th}$ that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to bendamustine.

Results of a human mass balance study confirm that bendamustine is extensively metabolized via hydrolytic, oxidative, and conjugative pathways.

In vitro studies using human liver microsomes indicate that bendamustine does 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 enzymes in primary cultures of human hepatocytes.

Elimination

Mean recovery of total radioactivity in cancer patients following IV infusion of [^{14}C] bendamustine hydrochloride was approximately 76% of the dose. Approximately 50% of the dose was recovered in the urine and approximately 25% of the dose was recovered in the feces. Urinary excretion was confirmed as a relatively minor pathway of elimination of bendamustine, with approximately 3.3% of the dose recovered in the urine as parent. 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.

Bendamustine clearance in humans is approximately 700 mL/minute. After a single dose of 120 mg/m^2 bendamustine IV over 1-hour the intermediate $t_{½}$ of the parent compound is approximately 40 minutes. The mean apparent terminal elimination $t_{½}$ of M3 and M4 are approximately 3 hours and 30 minutes respectively. Little or no accumulation in plasma is expected for bendamustine administered on Days 1 and 2 of a 28-day cycle.

Renal Impairment

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of renal impairment (CrCL 40 - 80 mL/min, N=31) on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with CrCL < 40 mL/min.

These results are however limited, and therefore bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < 40 mL/min. *[see Use in Specific Populations (8.6)]*

Hepatic Impairment

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of mild (total bilirubin ≤ ULN, AST ≥ ULN to 2.5 x ULN, and/or ALP ≥ ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment.

These results are however limited, and therefore bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5 - 10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment. *[see Use in Specific Populations (8.7)]*

Effect of Age

Bendamustine exposure (as measured by AUC and C_{max}) has been studied in adult patients ages 31 through 84 years. The pharmacokinetics of bendamustine (AUC and C_{max}) were not significantly different between patients less than or greater than/equal to 65 years of age. *[see Use in Specific Populations (8.4, 8.5)]*

Effect of Gender

The pharmacokinetics of bendamustine were similar in male and female patients. *[see Use in Specific Populations (8.8)]*

Effect of Race

The effect of race on the safety, and/or efficacy of TREANDA has not been established. Based on a cross-study comparison, Japanese subjects (n = 6) had on average exposures that were 40% higher than non-Japanese subjects receiving the same dose. The significance of this difference on the safety and efficacy of TREANDA in Japanese subjects has not been established.

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 (12.5 mg/kg/day, the lowest dose tested) and 75 mg/m^2/day (25 mg/kg/day) for four days, peritoneal sarcomas in female AB/jena mice were produced. Oral administration at 187.5 mg/m^2/day (62.5 mg/kg/day, the only dose tested) for four days induced mammary carcinomas and pulmonary adenomas.

Bendamustine is a mutagen and clastogen. In a reverse bacterial 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.

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.

14 CLINICAL STUDIES

14.1 Chronic Lymphocytic Leukemia (CLL)

The safety and efficacy of TREANDA were evaluated in an open-label, randomized, controlled multicenter trial comparing TREANDA to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - 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 TREANDA 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 65.7x10^9/L vs. 65.1x10^9/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 TREANDA 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 TREANDA compared to chlorambucil (see Table 5). Survival data are not mature.

Table 5: Efficacy Data for CLL

	TREANDA (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 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin > 110g/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.

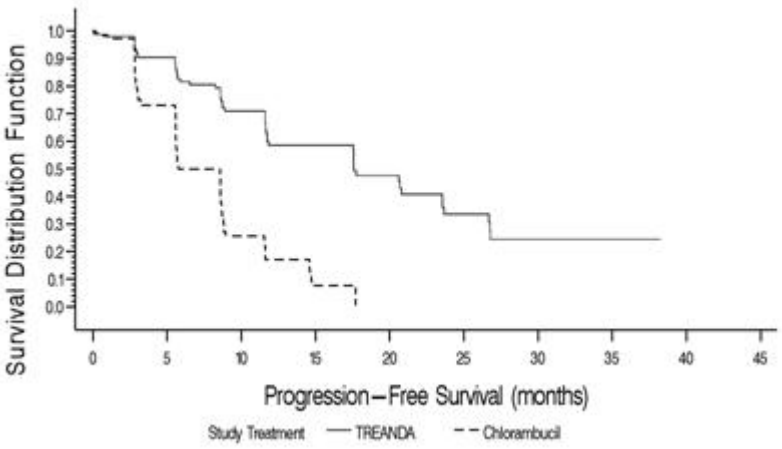
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

† 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 >110g/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 TREANDA with chlorambucil are shown in Figure 1.

Figure 1. Progression-Free Survival



14.2 Non-Hodgkin Lymphoma (NHL)

The efficacy of TREANDA 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 TREANDA 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*

	TREANDA (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*. [Accessed on July 21, 2015, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

TREANDA is a cytotoxic drug. Follow applicable special handling and disposal procedures[1]. Care should be exercised in the handling and preparation of solutions prepared from TREANDA Injection and TREANDA for Injection. 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 TREANDA Injection prior to dilution, remove gloves and follow disposal procedures[1]. If a solution of TREANDA contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA contacts the mucous membranes, flush thoroughly with water.

16.2 How Supplied

TREANDA (bendamustine hydrochloride) Injection is supplied as a 90 mg/mL clear colorless to yellow solution in individual cartons as follows:

- NDC 63459-395-02: 45 mg/0.5 mL of solution in an amber single-dose vial
- NDC 63459-396-02: 180 mg/2 mL of solution in an amber single-dose vial

TREANDA (bendamustine hydrochloride) for Injection is supplied in individual cartons as follows:

- NDC 63459-390-08: 25 mg white to off-white lyophilized powder in a 8 mL amber single-dose vial
- NDC 63459-391-20: 100 mg white to off-white lyophilized powder in a 20 mL amber single-dose vial

16.3 Storage

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution)

TREANDA Injection must be stored refrigerated between 2-8°C (36-46°F). Retain in original package until time of use to protect from light.

TREANDA for Injection (25 mg/vial or 100 mg/vial lyophilized powder)

TREANDA for Injection 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.

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 Adverse Reactions (5.3)]*.

Myelosuppression

Inform patients of the likelihood that TREANDA 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 Adverse Reactions (5.1)]*.

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 (5.6)]*.

Fatigue

Advise patients that TREANDA 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 TREANDA 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 TREANDA 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 TREANDA. Advise patients to immediately report severe or worsening rash or itching *[see Warnings and Precautions (5.5)]*.

Pregnancy and Nursing

TREANDA can cause fetal harm. Women should be advised to avoid becoming pregnant throughout treatment and for 3 months after TREANDA therapy has stopped. Men receiving TREANDA should use reliable contraception for the same time period. Advise patients to report pregnancy immediately. Advise patients to avoid nursing while receiving TREANDA *[see Use in Specific Populations (8.1)]*.

TRE-XXX

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