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) for Injection, for intravenous infusion
Initial U.S. Approval: 2008

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

Dosage and Administration, General Considerations for Tumor Lysis Syndrome (2.3) – Subsection deleted	04/2009
Dosage and Administration, Reconstitution/Preparation for Intravenous Administration (2.3)	04/2009
Warnings and Precautions, Tumor Lysis Syndrome (5.4)	04/2009
Warnings and Precautions, Skin Reactions (5.5)	04/2009
Warnings and Precautions, Extravasation (5.7)	01/2010

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

TREANDA 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's lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. (1.2)

----------DOSAGE AND ADMINISTRATION----------

For CLL:

- 100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles (2.1)
- Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce dose to 50 mg/m^2 on Days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m^2 on Days 1 and 2. (2.1)
- Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle. (2.1)
- Dose re-escalation may be considered. (2.1)

For NHL:

- 120 mg/m^2 infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles (2.2)
- Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. (2.2)
- Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. (2.2)

General Dosing Considerations:

- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. (2.1, 2.2)
- TREANDA for Injection must be reconstituted and further diluted prior to infusion. (2.3)

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

TREANDA for Injection single-use vial containing either 25 mg or 100 mg of bendamustine HCl as lyophilized powder (3)

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

Known hypersensitivity to bendamustine or mannitol. (4)

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

- Myelosuppression: May warrant treatment delay or dose reduction. Monitor closely and restart treatment based on ANC and platelet count recovery. Complications of myelosuppression may lead to death. (5.1)
- Infections: Monitor for fever and other signs of infection and treat promptly. (5.2)
- Infusion Reactions and Anaphylaxis: Severe anaphylactic reactions have occurred. Monitor clinically and discontinue drug for severe reactions. Ask patients about reactions after the first cycle. Consider pre-treatment for cycles subsequent to milder reactions. (5.3)
- Tumor Lysis Syndrome: May lead to acute renal failure and death. Take precautions in patients at high risk. (5.4)
- Skin Reactions: Discontinue for severe skin reactions. Cases of SJS and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. (5.5)
- Other Malignancies: Pre-malignant and malignant diseases have been reported. (5.6)
- Extravasation: Take precautions to avoid extravasation, including monitoring intravenous infusion site during and after administration. (5.7)
- Use in Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving TREANDA. (5.8, 8.1)

----------ADVERSE REACTIONS----------

Most common non-hematologic adverse reactions for CLL (frequency ≥15%) are pyrexia, nausea, and vomiting. (6.1)

Most common non-hematologic adverse reactions for NHL (frequency ≥15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. (6.2)

Most common hematologic abnormalities for both indications (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Cephalon, Inc., at 1-800-896-5855 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 02/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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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's Lymphoma (NHL)

TREANDA for Injection is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions for CLL

Recommended Dosage:

The recommended dose is 100 mg/m^2 administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

Dose Delays, Dose Modifications and Reinitiation of Therapy for CLL:

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.

2.2 Dosing Instructions for NHL

Recommended Dosage:

The recommended dose is 120 mg/m^2 administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Dose Delays, Dose Modifications and Reinitiation of Therapy for NHL:

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.

2.3 Reconstitution/Preparation for Intravenous Administration

- Aseptically reconstitute each TREANDA vial as follows:
  - 25 mg TREANDA vial: Add 5 mL of only **Sterile Water for Injection, USP**.
  - 100 mg TREANDA 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. 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. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. After transferring, thoroughly mix the contents of the infusion bag. 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.

2.4 Admixture Stability

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

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 refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of TREANDA must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

TREANDA for Injection single-use vial containing either 25 mg or 100 mg of bendamustine HCl as white to off-white lyophilized powder.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Patients treated with TREANDA are likely to experience myelosuppression. In the two NHL studies, 98% of patients had Grade 3-4 myelosuppression (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 closely. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Hematologic nadirs may require dose delays if recovery to the recommended values have not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be $\geq 1 \times 10^9$/L and the platelet count should be $\geq 75 \times 10^9$/L. *[See Dosage and Administration (2.1) and (2.2)]*

5.2 Infections

Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with TREANDA are more susceptible to infections. Patients with myelosuppression following TREANDA treatment should be advised to contact a physician if they have symptoms or signs of infection.

5.3 Infusion Reactions and Anaphylaxis

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. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome associated with TREANDA treatment has been reported in patients in clinical trials and in post-marketing 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 maintaining adequate volume status, 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

A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when TREANDA was given in combination with other anticancer agents, so the precise relationship to TREANDA is uncertain.

In a study of TREANDA (90 mg/m^2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert). Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to TREANDA cannot be determined.

Where skin reactions occur, they may be progressive and increase in severity with further treatment. Therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, TREANDA should be withheld or discontinued.

5.6 **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. The association with TREANDA therapy has not been determined.

5.7 **Extravasation**

There are postmarketing reports of bendamustine extravasations resulting in hospitalizations from erythema, marked swelling, and pain. Precautions should be taken to avoid extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of TREANDA.

5.8 **Use in Pregnancy**

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 data described below reflect exposure to TREANDA in 349 patients who participated in an actively-controlled trial (N=153) for the treatment of CLL and two single-arm studies (N=176) for the treatment of indolent B-cell NHL. 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.

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)]*
- Infusion Reactions and Anaphylaxis *[See Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[See Warnings and Precautions (5.4)]*
- Skin Reactions *[See Warnings and Precautions (5.5)]*
- Other Malignancies *[See Warnings and Precautions (5.6)]*

6.1 **Clinical Trials Experience in CLL**

The data described below reflect exposure to TREANDA in 153 patients. TREANDA was studied in an active-controlled trial. The population was 45-77 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 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 randomized CLL clinical study and 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				
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 TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

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