TREANDA® (bendamustine hydrochloride) injection, for intravenous use

TREANDA® (bendamustine hydrochloride) for injection, for intravenous use

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)

Dosing and Administration

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

- For CLL:
  - 100 mg/m² infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles (2.2)
  - 120 mg/m² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles (2.3)

- For NHL:
  - 45 mg/0.5 mL or 180 mg/2 mL (90 mg/mL) in a single-dose vial. (3)

Contraindications

TREANDA is contraindicated in patients with a history of a hypersensitivity reaction to bendamustine. Reactions have included anaphylaxis and anaphylactoid reactions. (4, 5.3)

Warnings and Precautions

- 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. (5.3)
- Tumor Lysis Syndrome: May lead to acute renal failure and death; anticipate and use supportive measures in patients at high risk. (5.4)
- Skin Reactions: Discontinue for severe skin reactions. Cases of SJS, DRESS and TEN, some fatal, have been reported. (5.5)
- Hepatotoxicity: Monitor liver chemistry tests prior to and during treatment. (5.6)
- Extravasation Injury: Take precautions to avoid extravasation, including monitoring intravenous infusion site during and after administration. (5.8)
- 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. (5.9, 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. (6.2, 6.3)
- Most common adverse reactions (≥15%) for NHL are lymphopenia, leukopenia, anemia, neutropenia, thrombocytopenia, anemia, thrombocytopenia, nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. (6.2, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions

Consider alternative therapies that are not CYP1A2 inducers or inhibitors during treatment with TREANDA. (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 1.5-3 x ULN and AST or ALT 2.5-10 x ULN, or total bilirubin >3 x ULN. (8.7)

See 17 for Patient Counseling Information

Full Prescribing Information: Contents*

1 Indications and Usage
2 Dosing and Administration
3 Dose Forms and Strengths
4 Contraindications
5 Warnings and Precautions
6 Adverse Reactions
7 Drug Interactions
8 Use in Specific Populations
9 Use in Elderly Patients
10 Overdose
11 Description
12 Clinical Pharmacology
13 Nonclinical Toxicology
14 Clinical Studies
15 References
16 How Supplied/Storage and Handling
17 Patient Counseling Information

*Sections or subsections omitted from the full prescribing information are not listed.
TREANDA® (bendamustine hydrochloride) injection
TREANDA® (bendamustine hydrochloride) for injection

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 CSTD, 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 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, only use TREANDA for Injection, the lyophilized powder formulation [see How Supplied/Storage and Handling (16.1)].

2.2 Dosing Instructions for CLL

Recommenced Dose:
The recommended dose is 100 mg/m² 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 TREANDA 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 × 10⁹/L, platelets ≥ 75 × 10⁹/L], reinitiate TREANDA 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/m² on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m² on Days 1 and 2 of each cycle. Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m² on Days 1 and 2 of each cycle. Consider dose re-escalation in subsequent cycles at the discretion of the treating physician.

2.3 Dosing Instructions for NHL

Recommended Dose:
The recommended dose is 120 mg/m² 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 TREANDA 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 × 10⁹/L, platelets ≥ 75 × 10⁹/L], reinitiate TREANDA 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 90 mg/m² on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle. Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle.

2.4 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. If 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.

• When preparing and transferring the concentrated TREANDA Injection solution into the infusion bag, do not use devices that contain polycarbonate or ABS.

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 CSTD, 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 infusate bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible with TREANDA Injection 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 preparation¹, only use TREANDA for Injection, the lyophilized powder formulation [see How Supplied/Storage and Handling (16.1)].

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 infusate 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 with TREANDA for Injection.

TREANDA Injection must be completed within this period.

• Shake well to yield a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL and the concentration of bendamustine hydrochloride in the infusion bag should be within 0.2 – 0.7 mg/mL.

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 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 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 diluted TREANDA Injection must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

• TREANDA Injection: 45 mg/0.5 mL or 180 mg/2 mL as a clear and colorless to yellow ready-to-dilute solution 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 ADVERSE REACTIONS

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 and pneumonia from an opportunistic infection (CMV).

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 neutrophils frequently. In the clinical trials, blood counts were monitored every week. Initially hematologic nadirs were observed within 10 to 28 days 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 x 10^9/L and the platelet count should be ≥75 x 10^9/L. [see Dosage and Administration (2.2) and (2.3)]

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. Alopecinol 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 antineoplastic agents. 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. The association with bendamustine hydrochloride therapy has not been determined.

5.8 Extravasation Injury
TREANDA extravasations have been reported in postmarketing 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
Based on findings from animal reproduction studies and the drug's mechanism of action, TREANDA 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 TREANDA and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TREANDA and for at least 3 months after the final dose. [see Use in Specific Populations (8.1, 8.3) and ClinicalPharmacology (12.1)]

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

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. TREANDA was studied in an active-controlled, randomized 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 v2.0. 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 in none treated with chlorambucil. Three of these 4 adverse reactions were described as a hypertensive crisis and were managed with antihypertensives and resolution and resolved.

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in a 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

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TREANDA (N=153)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (20)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (16)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (9)</td>
</tr>
<tr>
<td>General disorders and</td>
<td></td>
</tr>
<tr>
<td>administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36 (24)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Infection</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Investigations</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td>11 (7)</td>
</tr>
</tbody>
</table>

continued
TREANDA® (bendamustine hydrochloride) injection
TREANDA® (bendamustine hydrochloride) for injection

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TREANDA (N=150)</th>
<th>Chlorambucil (N=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
<td>Grade 3/4 n (%)</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>134 (89)</td>
<td>20 (13)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>116 (77)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Leukocytes Decreased</td>
<td>92 (61)</td>
<td>42 (28)</td>
</tr>
<tr>
<td>Lymphocytes Decreased</td>
<td>102 (68)</td>
<td>70 (47)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>113 (75)</td>
<td>65 (43)</td>
</tr>
</tbody>
</table>

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/m² 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 (N=176)

<table>
<thead>
<tr>
<th>Body System /Adverse Reaction</th>
<th>Number (%) of patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Total number of patients with at least 1 adverse reaction</td>
<td>176 (100)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>132 (75)</td>
</tr>
<tr>
<td>Nausea</td>
<td>71 (40)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>65 (37)</td>
</tr>
<tr>
<td>Constipation</td>
<td>51 (29)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>27 (15)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>20 (11)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>8 (5)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>101 (57)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>59 (34)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24 (14)</td>
</tr>
<tr>
<td>Chills</td>
<td>23 (13)</td>
</tr>
<tr>
<td>Assthenia</td>
<td>19 (11)</td>
</tr>
</tbody>
</table>

*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%), hypokalemia (2%), and hypocalcemia (2%).

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

<table>
<thead>
<tr>
<th>Hematology variable</th>
<th>TREANDA (%)</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes Decreased</td>
<td>99</td>
<td>94</td>
</tr>
<tr>
<td>Leukocytes Decreased</td>
<td>94</td>
<td>56</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>88</td>
<td>11</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>86</td>
<td>60</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>86</td>
<td>25</td>
</tr>
</tbody>
</table>

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.
TREANDA® (bendamustine hydrochloride) injection
TREANDA® (bendamustine hydrochloride) for injection

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, dysgeusa/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 system 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: Pneumonia

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

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on TREANDA

CYP1A2 inhibitors

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

CYP1A2 inducers

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

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%-4% and 15%-20%, respectively.

Data

Animal data

Bendamustine hydrochloride was intraperitoneally administered once to mice from 210 mg/m2 (approximately 1.8 times the MRHD) during organogenesis and caused an increase in resorptions, skeletal and visceral malformations (encephaly, cleft palate, 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 7-11 resulted in an increase in resorptions from 75 mg/m2 (approximately 0.6 times the MRHD) and an increase in abnormalities from 112.5 mg/m2 (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/m2 (approximately the MRHD) on gestation days 4, 7, 9, 11, or 13 and caused embryo/foetal mortality 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 (hydrocephrosis 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 TREANDA, and for at least 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

TREANDA can cause fetal harm when administered to a pregnant woman [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)].

8.3.1 Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiation of treatment with TREANDA.
The mean steady-state volume of distribution (Vss) of bendamustine was approximately 20-25 L. The protein binding of bendamustine ranged from 94-96% and was concentration dependent. The dose proportionality of bendamustine has not been studied.

rituximab at 375 mg/m² intravenous infusion followed by a 30-minute intravenous infusion of bendamustine at 90 mg/m²/day. No mean changes greater than 12.2 pharmacodynamic pathways. Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like ring. Mechloretamine 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.

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

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/m² intravenous infusion followed by a 30-minute intravenous infusion of bendamustine at 90 mg/m²/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 is unknown.

12 Pharmacokinetics
Absorption
Following a single IV dose of bendamustine hydrochloride Cmax, typically occurred at the end of infusion. The dose proportionality of bendamustine has not been studied.

Distribution
The protein binding of bendamustine ranged from 94-96% and was concentration independent from 1-50 μg/mL. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.66 over a concentration range of 10 to 100 μg/mL. The mean steady-state volume of distribution (Vss) of bendamustine was approximately 20-25 L.

Elimination
After a single intravenous dose of 120 mg/m² of bendamustine over 1 hour, the intermediate half-life (t1/2) of the parent compound is approximately 40 minutes. The mean terminal elimination t1/2 of two active metabolites, γ-hydroxybendamustine (M3) and N-demethylbendamustine (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 N-demethylbendamustine (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 IV 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 x ULN and AST or ALT ≤ 2.5 x ULN. The effects of severe renal impairment (Clcr < 30 mL/min), or hepatic impairment with total bilirubin 1.5-3 x ULN or AST or ALT 2.5-10 x ULN or total bilirubin > 3 x 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, CYP2C9, 10, 26, 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/m²/day (the lowest dose tested, approximately 0.3 times the maximum recommended human dose [MRHD]) and 75 mg/m²/day (approximately 0.6 times the MRHD of maximum recommended daily dose) for 24 days, tumors in female mice were produced. Ovarian administration at 187.5 mg/m²/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/m² (the lowest dose tested, approximately 0.3 times the MRHD).

Bendamustine induced morphologic abnormalities in spermatocytes in mice. Following a single iv injection of bendamustine at 120 mg/m² or a saline control on days 1 and 2 for a total of 3 weeks, the number of spermatocytes 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 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 without evidence of disease, 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 liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), “B” symptoms (51% vs. 53%), lymphocyte count (mean 65.7x10⁹/L vs. 65.1x10⁹/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immunophenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either TREANDA at 100 mg/m², 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

<table>
<thead>
<tr>
<th></th>
<th>TREANDA (N=153)</th>
<th>Chlorambucil (N=148)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>90 (59)</td>
<td>38 (26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(51.0, 66.6)</td>
<td>(18.6, 32.7)</td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)*</td>
<td>13 (8)</td>
<td>1 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Partial response (nPR)**</td>
<td>4 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)†</td>
<td>73 (48)</td>
<td>37 (25)</td>
<td></td>
</tr>
<tr>
<td>Progression-Free Survival††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>18 (11.7, 23.5)</td>
<td>6 (5.6, 8.6)</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.27 (0.17, 0.45)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* CR was defined as peripheral lymphocyte count ≤ 4.0 x 10⁹/L, neutrophils ≥ 1.5 x 10⁹/L, platelets >100 x 10⁹/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 10⁹/L, platelets >100 x 10⁹/L, hemoglobin >110g/L, without transfusions, 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.

CL = confidence interval
CR = complete response
nPR = near complete response
PR = partial response
PFS = 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/m² 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 alkylator therapy, 91% of patients had received previous alkylation 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*

<table>
<thead>
<tr>
<th>Response Rate (%)</th>
<th>TREANDA (N=100)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (CR+CRu+PR)</td>
<td>74</td>
<td>(64.3, 82.3)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Complete response unconfirmed (CRu)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

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


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

TREANDA (bendamustine hydrochloride) is a cytotoxic drug. Follow applicable special handling and disposal procedures. 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. If a solution of TREANDA (bendamustine hydrochloride) contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA (bendamustine hydrochloride) 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 63459-390-08: 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