TREANDA® (bendamustine hydrochloride) for injection

**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/m² infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles (2.2)

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

**DOSAGE FORMS AND STRENGTHS**

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

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

**WARNINGS AND PRECAUTIONS**

**- Myelosuppression**: Delay or reduce dose and restart treatment based on ANC and platelet count recovery. (5.1)
- **Infections**: Monitor for fever and other signs of infection or reactivation of infections and treat promptly. (5.2)
- **Progressive multifocal leukoencephalopathy (PML)**: Monitor for new or worsening neurological, cognitive or behavioral signs or symptoms suggestive of PML. (5.3)
- **Neurological, cognitive or behavioral signs or symptoms suggestive of PML**: Monitor for new or worsening neurological, cognitive or behavioral signs or symptoms suggestive of PML. (5.3)
- **Lymphopenia, leukopenia, anemia, neutropenia, lymphopenia, leukopenia, pyrexia, nausea, vomiting**: (6.1, 6.2)
- **Nausea and fatigue**: (6.1)

**- Adverse reactions**

- Adverse reactions (frequency >5%) during infusion and within 24 hours post-infusion are nausea and fatigue. (6.1)
- Most common adverse reactions (≥15%) for CLL are anemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, pyrexia, nausea, vomiting. (6.1, 6.2)
- Most common adverse reactions (≥15%) for NHL are lymphopenia, leukopenia, anemia, neutropenia, lymphocytopenia, pyrexia, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. (6.1, 6.2)

**- Anaphylaxis and infusion reactions**: Severe and anaphylactic reactions have occurred; monitor clinically and discontinue drug for severe reactions. Pre-medicate in subsequent cycles for milder reactions. (5.4)
- **Tumor lysis syndrome**: May lead to acute renal failure and death; anticipate and use supportive measures in patients at high risk. (5.5)
- **Skin reactions**: Discontinue for severe skin reactions. Cases of SJS, DRESS and TEN, some fatal, have been reported. (5.6)
- **Hepatotoxicity**: Monitor liver chemistry tests prior to and during treatment. (5.7)
- **Other malignancies**: Pre-malignant and malignant diseases have been reported. (5.8)
- **Extravasation injury**: Take precautions to avoid extravasation, including monitoring intravenous infusion site during and after administration. (5.9)
- **Embryo-Fetal Toxicity**: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception. (5.10, 8.1, 8.3)

**ADVERSE REACTIONS**

- Adverse reactions (frequency >5%) during infusion and within 24 hours post-infusion are nausea and fatigue. (6.1)
- Most common adverse reactions (≥15%) for CLL are anemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, pyrexia, nausea, vomiting. (6.1, 6.2)
- Most common adverse reactions (≥15%) for NHL are lymphopenia, leukopenia, anemia, neutropenia, lymphocytopenia, pyrexia, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. (6.1, 6.2)

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 ≥3 x ULN and AST or ALT ≥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
1.1 Chronic Lymphocytic Leukemia (CLL)
1.2 Non-Hodgkin Lymphoma (NHL)

2 DOSAGE AND ADMINISTRATION
2.1 Selection of TREANDA Formulation to Administer
2.2 Dosing Instructions for CLL
2.3 Dosing Instructions for NHL
2.4 Preparation for Intravenous Administration
2.5 Admixture Stability

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
5.1 Myelosuppression
5.2 Infections
5.3 Progressive Multifocal Leukoencephalopathy (PML)
5.4 Anaphylaxis and Infusion Reactions
5.5 Tumor Lysis Syndrome
5.6 Skin Reactions
5.7 Hepatotoxicity
5.8 Other Malignancies
5.9 Extravasation Injury
5.10 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on TREANDA

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
14.1 Chronic Lymphocytic Leukemia (CLL)
14.2 Non-Hodgkin Lymphoma (NHL)

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

Revised: 10/2022
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 syringe to withdraw from the vial into the infusion bag, only use a polypyrrole syringe with a metal needle and polypyrrole hub to withdraw and transfer TREANDA Injection into the infusion bag. Polypyrrole 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 bio-safety cabinet (BSC) or containment isolator using a polypyrrole syringe with a metal needle and a polypyrrole 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)].

2.2 Dosing Instructions for CLL

Recommended Dosing:
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 x 10⁹/L, platelets ≥ 75 x 10⁹/L], reinstate 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 Dosing:
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 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 10⁹/L, platelets ≥ 75 x 10⁹/L], reinstate 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 4 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 ≤ 80 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 hazardous drug. Follow applicable special handling and disposal procedures. [see Dosage and Administration (4.5)].

TREANDA Injection must be diluted in a bio-safety 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 adverse health consequences to the practitioner, including skin reactions; or to the patient, including but not limited to, the risk of 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 polypyrrole syringe with a metal needle and a polypyrrole hub to withdraw and transfer TREANDA Injection into the infusion bag.

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.

2.4 Preparation for Intravenous Administration

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.
5.2 Infections
Infection, including pneumonia, sepsis, septic shock, hepatitis and death has occurred in adult and pediatric patients in clinical trials and in postmarketing reports [see Adverse Reactions (6.1), (6.2)]. Patients with myelosuppression following treatment with TREANDA are more susceptible to infection. Advise patients 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 Progressive Multifocal Leukoencephalopathy (PML)
Progressive multifocal leukoencephalopathy (PML), including fatal cases, have occurred following treatment with bendamustine, primarily in combination with rituximab or obinutuzumab [see Adverse Reactions (6.2)]. Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected, withhold TREANDA treatment and perform appropriate diagnostic evaluations. Consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.4 Anaphylaxis and Infusion Reactions
Infusion reactions to TREANDA have occurred commonly in clinical trials [see Adverse Reactions (6.1)]. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients with Grade 1 or 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.

5.5 Tumor Lysis Syndrome
Tumor lysis syndrome associated with TREANDA treatment has occurred in patients in clinical trials and in postmarketing reports [see Adverse Reactions (6.1)]. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventing hyperuricemia with 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 (5.6)].

5.6 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 [see Adverse Reactions (6.1), (6.2)]. 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.

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

5.8 Other Malignancies
There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with TREANDA, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, bronchial carcinoma, and non-melanoma skin cancer, including basal cell carcinoma and squamous cell carcinoma [see Adverse Reactions (6.2)]. Monitor patients for the development of secondary malignancies. Perform dermatologic evaluations during and after treatment with TREANDA.

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

5.10 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 effects. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective method of contraception during treatment with TREANDA and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TREANDA and for 3 months after the last dose [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.2)]

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.

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

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Chronic Lymphocytic Leukemia
The data described below reflect exposure to 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 naive CLL. All patients started the study at a dose of 100 mg/m² 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 oral medications and resolved. The most frequent adverse reactions leading to study withdrawal for patients receiving TREANDA were hypersensitivity (2%) and pyrexia (5%).

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were observed 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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TREANDA (N=153)</td>
</tr>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Total number of patients with at least 1 adverse reaction</td>
<td>121 (79)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>31 (20)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (16)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Investigations</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>

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 with 6% of patients receiving chlorambucil.
Table 3: Non-Hematologic Adverse Reactions Occurring in at Least 5% of NHL Patients

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TREANDA</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hematologic Grade 3 or 4 adverse reactions (≥5%)</td>
<td>113 (75)</td>
<td>65 (43)</td>
</tr>
<tr>
<td>Fatigue (≥5%)</td>
<td>101 (62)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Febrile neutropenia (≥5%)</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>115 (77)</td>
<td>10 (1)</td>
</tr>
</tbody>
</table>

In the randomized CLL trial, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of Grade 3 or 4 were limited to 1% and 3% of patients, respectively. Patients treated with 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/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>Tachycardia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
</tr>
<tr>
<td></td>
<td>Infusion site pain</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Catheter site pain</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td></td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</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 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

<table>
<thead>
<tr>
<th>Hematology variable</th>
<th>All Grades</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, hypertension, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome. Serious drug-related adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumor lysis syndrome and infusion reactions. Adverse reactions occurring less frequently but possibly related to 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)
TREANDA® (bendamustine hydrochloride) injection
TREANDA® (bendamustine hydrochloride) for injection

Immune system disorders: Anaphylaxis
Infections and infestations: Pneumocystis jiroveci pneumonia, progressive multifocal leukoencephalopathy (PML)
Renal and urinary disorders: Nephrogenic diabetes insipidus (NDI)
Respiratory and muscular disorders: Pneumonitis
Skin and subcutaneous tissue disorders: Drug reaction with eosinophilia and systemic symptoms (DRESS), non-melanoma skin cancer (NMSC), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on TREANDA
CYP450 Inhibitors
The coadministration of TREANDA with CYP3A4 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 CYP3A4 inhibitors during treatment with TREANDA.

CYP450 Inducers
The coadministration of TREANDA with CYP3A4 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 CYP3A4 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 to 4% and 15 to 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 (exencephaly, 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 to 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, 11, or 13 and caused embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in external (on tail, head, and herniation of external organs [eosophagel]) and internal (hydropneumatisis and hydropneumothorax) malformations were seen in treated 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 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 Use in Specific Populations (8.1)].

Pregnancy Testing
Pregnancy testing is recommended for females of reproductive potential prior to initiation of treatment with TREANDA.

Contraception
Females
TREANDA can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment with TREANDA and for 6 months after the last dose [see Nonclinical Toxicology (13.3)].

Infertility
Males
Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with TREANDA for 3 months after the last dose [see Nonclinical Toxicology (13.3)].

8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
8.8 Drug Interactions

8.9 Pregnancy Testing
Pregnancy testing is recommended for females of reproductive potential prior to initiation of treatment with TREANDA.

Contraception
Females
TREANDA can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment with TREANDA and for 6 months after the last dose [see Nonclinical Toxicology (13.3)].

Infertility
Males
Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with TREANDA for 3 months after the last dose [see Nonclinical Toxicology (13.3)].

8.10 OVERDOSAGE
The intravenous LD₅₀ of bendamustine HCl is 240 mg/m² 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/m². 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), sinu 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 overdose should include general supportive measures, including monitoring of hemotologic parameters and ECGs.

II. DESCRIPTION
TREANDA (bendamustine hydrochloride) is an alkylating agent. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butonic acid, 5-[bis-(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is C₂₈H₂₀Cl₂N₄O₂.HCl, and the molecular weight is 594.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:

![structural formula of bendamustine hydrochloride](attachment://structural_formula.png)

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution)
TREANDA (bendamustine HCl) Injection for intravenous use is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single-dose vial. Each 25-mg vial contains 45 mg of bendamustine hydrochloride, 162 mg of Propylene Glycol, USP and 233 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 for intravenous use is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single-dose vial. Each 25-mg vial contains 25 mg of bendamustine hydrochloride 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 to 3.5.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkylic acid groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand 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 Cₘₚₐₚ. 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 was not evaluated.

12.3 Pharmacokinetics
Absorption
Following a single IV dose of bendamustine hydrochloride Cₘₚₐₚ typically occurred at the end of infusion. The dose proportionality of bendamustine has not been studied.
14.1 Chronic Lymphocytic Leukemia (CLL)

The safety and efficacy of TREANDA were evaluated in an open-label, randomized, controlled multicenter trial comparing TREANDA and 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), lymphoma stage (73% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (73% vs. 72%), “B” symptoms (50% vs. 53%), lymphocyte count (mean 6,250 x 10^9/L vs. 6,500 x 10^9/L), and serum lactate dehydrogenase (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had received previous chemotherapy, 91% of patients had received previous alkylator therapy, 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 Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. 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 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.

Response Rate (%)

<table>
<thead>
<tr>
<th>Study Treatment</th>
<th>TREANDA (N=148)</th>
<th>Chlorambucil (N=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (CR+PR)</td>
<td>74</td>
<td>60</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Complete response unconfirmed (CRu)</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>57</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 6: Efficacy Data for NHL

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.
safe handling and disposal

TREANDA (bendamustine hydrochloride) is a hazardous 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.

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

Storage

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

Store TREANDA injection in refrigerator 2°C to 8°C (36°F to 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

18.6 Allergic (Hypersensitivity) Reactions

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

Myelosuppression

Inform patients of the likelihood that 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 Warnings and Precautions (5.5)].

Progressive Multifocal Leukoencephalopathy (PML)

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

Hepatotoxicity

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

Fatigue

Advise patients that 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 (5.6)].

Non-Melanoma Skin Cancer (NMSC)

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

Embryo-Fetal Toxicity

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

Lactation

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