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)

**DOSE 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). (CSTD).

**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**

- Infections: Monitor for fever and other signs of infection or reactivation of infections and treat promptly. (5.2)
- Anaphylaxis and Infusion Reactions: Severe and anaphylactic reactions have occurred; monitor clinically and discontinue 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 anemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, pyrexia, nausea, vomiting. (6.2, 6.3)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.2 Lactation
8.3 Males and Females 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

16.1 Safe Handling and Disposal
16.2 How Supplied
16.3 Storage

17 PATIENT COUNSELING INFORMATION

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

2.2 Dosing Instructions for CLL
[see How Supplied/Storage and Handling (16.1)]

2.2.1 Dosing Instructions for CLL
Recommended Dosage:
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:
[see Dosage and Administration (2.4)]

If Grade 3 or greater non-hematologic toxicity recurs, reduce the dose to 50 mg/m² on Days 1 and 2 of each cycle.

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 a CSTD or adapter that contains polycarbonate or ABS is used as supplemental protection prior to dilution¹, only use TREANDA for Injection, the lyophilized powder formulation [see How Supplied/Storage and Handling (16.1)].

2.2.2 Dosing Instructions for NHL
Recommended Dosage:
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:
[see Warnings and Precautions (5.1)]

2.2.3 Preparation for Intravenous Administration
TREANDA is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution)
TREANDA Injection must be diluted in a biosafety cabinet (BSC) or containment isolator.

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

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

If a CSTD or adapter that contains polycarbonate or ABS is used as supplemental protection prior to dilution¹, only use TREANDA for Injection, the lyophilized powder formulation [see How Supplied/Storage and Handling (16.1)].

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.

Delay TREANDA administration in the event of a Grade 4 hematologic toxicity or toxicity has recovered to less than or equal to Grade 1 and/or the blood counts have clinically significant

Delay TREANDA administration in the event of Grade 4 hematologic toxicity or another toxicity has recovered to less than or equal to Grade 1 and/or the blood counts have clinically significant

Do not 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 a CSTD or adapter that contains polycarbonate or ABS is used as supplemental protection prior to dilution¹, only use TREANDA for Injection, the lyophilized powder formulation [see How Supplied/Storage and Handling (16.1)].
4 CONTRAINDICATIONS
TREANDA is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine [see Warnings and Precautions (5.3)].

5 WARNINGS AND PRECAUTIONS
5.1 Myelosuppression
TREANDA caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies and in 31% of patients in the randomized CLL study. Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

Monitor complete blood counts, including leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Initially, hematologic nadirs were observed predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be ≥1 x 10⁹/L and the platelet count should be ≥75 x 10⁹/L. [see Dosage and Administration (2.2) and (2.3)].

5.2 Infections
Infection, including pneumonia, sepsis, septic shock, hepatitis and death has occurred in adult and pediatric patients in clinical trials and in postmarketing reports. Patients with myelosuppression following treatment with TREANDA are more susceptible to infection. Advise patients to contact a physician if they have symptoms or signs of infection.

Patients treated with TREANDA are at risk for reactivation of infections including (but not limited to) hepatitis B, cytomegalovirus, Mycobacterium tuberculosis, and herpes zoster. Patients should undergo appropriate measures (including clinical and laboratory monitoring, prophylaxis, and treatment) for infection and infection reactivation prior to administration.

5.3 Anaphylaxis and Infusion Reactions
Infusion reactions to TREANDA have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experience Grade 3 or worse allergic-type reactions should not be challenged to prevent severe reactions, including anaphylaxis, angioedema, urticaria, anaphylactoid reactions, and thrombotic microangiopathy.

Monitor complete blood counts, including leukocytes, platelets, hemoglobin, and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Initially, hematologic nadirs were observed predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be ≥1 x 10⁹/L and the platelet count should be ≥75 x 10⁹/L. [see Dosage and Administration (2.2) and (2.3)].

5.4 Tumor Lysis Syndrome
Tumor lysis syndrome associated with TREANDA treatment has occurred in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of TREANDA therapy. However, there may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly [see Warnings and Precautions (5.5)].

5.5 Skin Reactions
Fatal and serious skin reactions have been reported with TREANDA treatment in clinical trials and postmarketing safety reports, including toxic skin reactions [Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)], bullous exanthema, and rash. Events occurred when TREANDA was given as a single agent and in combination with other anticancer agents. 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 adult and pediatric patients in clinical trials and postmarketing reports, including toxic skin reactions [Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)], bullous exanthema, and rash. Events occurred when TREANDA was given as a single agent and in combination with other anticancer agents. 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.

5.8 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
**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=153)</th>
<th>Chlorambucil (N=143)</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 reflects 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 fatigue (75%), nausea (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 n (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 3/4 n (%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>176 (100)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>132 (75)</td>
</tr>
<tr>
<td>Nausea</td>
<td>74 (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></td>
</tr>
<tr>
<td>Fatigue</td>
<td>101 (57)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>59 (34)</td>
</tr>
<tr>
<td>Chills</td>
<td>24 (14)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>23 (13)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19 (11)</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 compared with 6% of patients receiving chlorambucil.
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, 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 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: Pneumonitis

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 (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 7-11 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 and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in external (effect on tail, head, and herniation of external organs [exomphalos]) and internal (hydronephrosis and hydrocephalus) malformations were seen in dosed rats.

8.2 Lactation

Risk Summary

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

Pregnancy testing is recommended for females of reproductive potential prior to initiation of treatment with TREANDA.
TREANDA® (bendamustine hydrochloride) injection

TREANDA® (bendamustine hydrochloride) injection for injection

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

TREANDA (bendamustine HCI) Injection for intravenous use is supplied as a sterile clear colorless to yellow solution in a single-dose vial. Each 0.5 mL vial contains 45 mg of bendamustine hydrochloride, 162 mg of Propylene Glycol, USP and 293 mg of 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 - 3.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacokinetics

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

Cardiac Electrocardiology

The effect of bendamustine on the QTc interval was evaluated in 53 patients with idiopathic heart disease. Bendamustine did not alter QTc in healthy volunteers or in patients with chronic heart failure.

12.3 Pharmacodynamics

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 mean terminal elimination t½ of two active metabolites, M3 and M4, is 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 dehydrogenate (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 radio labeled bendamustine hydrochloride in cancer patients, approximately 76% of the dose was recovered. Approximately 50% of the dose was recovered in the urine (3.3% unchanged) and approximately 25% of the dose was recovered in the feces. Less than 1% of the dose was recovered in the urine as M3 and M4, and less than 5% of the dose was recovered in the urine as HP2.

Specific Populations

No clinically meaningful effects on the pharmacokinetics of bendamustine were observed based on age (31 to 84 years), sex, mild to moderate renal impairment (CLcr ≥ 30 mL/min), or hepatic impairment with total bilirubin 1.5 < ULN and AST or ALT < 2.5 × ULN. The effects of severe renal impairment (CLcr < 30 mL/min), or hepatic impairment with total bilirubin 1.5 × ULN and AST or ALT 2.5-5 × ULN or total bilirubin 3 × ULN on the pharmacokinetics of bendamustine is unknown.

Race/Ethnicity

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

Drug Interaction Studies

In Vitro Studies

Effect of bendamustine on CYP Substrates

Bendamustine did not inhibit CYP1A2, CYP2C9, 10, 26, 3, 1, or SULT/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) for 28 days per period, 50% of female mice and 25% of male mice were produced. Oral 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 spermatozoa in mice. Following tail vein 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 spermatoza 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 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 (76% vs. 80%), enlarged spleen (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), “B” symptoms (51% vs. 53%), lymphocyte count (mean 65.7±10/L vs. 65.1±10/L), and serum lactate dehydrogenase concentration (mean 370.2±388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either TREANDA at 100 mg/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>Endpoint</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>
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<tr>
<td>Complete response (CR)*</td>
<td>13 (8)</td>
<td>1 (&lt;1)</td>
<td></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>0.0001</td>
<td></td>
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</tbody>
</table>

CI = confidence interval

* CR was defined as peripheral lymphocyte count ≤ 4.0 x 10/L, neutrophils ≥ 1.5 x 10/L, platelets >100 x 10/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 for CR with the exception that the bone marrow biopsy shows persistent nodules.

† PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥ 50% reduction in lymphadenopathy, or ≥ 50% reduction in the size of spleen or liver; as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10/L, platelets >100 x 10/L, hemoglobin >110g/L, without transfusions. Progression-free survival based on baseline, platelets >100 x 10/L or 50% improvement over baseline, hemoglobin >110g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

¶ PFS was defined as time from randomization to progression or death from any cause.
TREANDA® (bendamustine hydrochloride) injection
TREANDA® (bendamustine hydrochloride) for injection

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

Figure 1. Progression-Free Survival

14.2 Non-Hodgkin Lymphoma (NHL)
The efficacy of TREANDA was evaluated in a single arm study of 100 patients with indolent B-cell NHL that had progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received TREANDA intravenously at a dose of 120 mg/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 chemotherapy, 91% of patients had received previous alkylator therapy, and 97% of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab.

Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfined + 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>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (CR+CRu+PR)</td>
<td>74 (64.3, 82.3)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>13</td>
</tr>
<tr>
<td>Complete response unconfirmed (CRu)</td>
<td>4</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>57</td>
</tr>
</tbody>
</table>

Duration of Response (DR)
Median, months (95% CI) 9.2 months (7.1, 10.8)

Cl = 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

16.3 Storage
TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) Store TREANDA injection in refrigerator 2° to 8°C (36° to 48°F). Retain in original package until time of use to protect from light. TREANDA for Injection (25 mg/vial or 100 mg/vial lyophilized powder) TREANDA for Injection may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) (see USP Controlled Room Temperature). Retain in original package until time of use to protect from light.

17 PATIENT COUNSELING INFORMATION
Allergic (Hypersensitivity) Reactions
Inform patients of the possibility of mild or serious allergic reactions and to immediately report rash, facial swelling, or difficulty breathing during or soon after infusion [see Warnings and Precautions (5.3)].

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

Hepatotoxicity
Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately contact their health care provider if signs of liver failure occur, including jaundice, anorexia, bleeding or bruising [see Warnings and Precautions (5.6)].

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

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

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

Rash
Advise patients that a rash or itching may occur during treatment with TREANDA. Advise patients to immediately report severe or worsening rash or itching [see Warnings and Precautions (5.5)].

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 (5.9), 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 at least 6 months after the final 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 at least 3 months after the final 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 at least 1 week after the final dose [see Use in Specific Populations (8.2)].

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