

EXHIBIT 2001

Cephalon Exhibit 2001
Fresenius v. Cephalon
IPR2016-00111

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

| | |
|--|---------|
| Dosage and Administration (2) | 09/2015 |
| Selection of TREANDA Formulation to Administer (2.1) | 09/2015 |
| Preparation for Intravenous Administration (2.4) | 09/2015 |
| Admixture Stability (2.5) | 03/2015 |
| Warnings and Precautions, Infections (5.2) | 11/2015 |

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)
- Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce dose to 50 mg/m² on Days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m² on Days 1 and 2. (2.2)
- Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m² on Days 1 and 2 of each cycle. (2.2)
- Dose re-escalation may be considered. (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)
- 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. (2.3)
- 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. (2.3)

General Dosing Considerations:

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

DOSAGE FORMS AND STRENGTHS

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

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

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- Chronic Lymphocytic Leukemia (CLL)
- Non-Hodgkin Lymphoma (NHL)

2 DOSAGE AND ADMINISTRATION

- Selection of TREANDA Formulation to Administer
- Dosing Instructions for CLL
- Dosing Instructions for NHL
- Preparation for Intravenous Administration
- Admixture Stability

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- Myelosuppression
- Infections
- Anaphylaxis and Infusion Reactions
- Tumor Lysis Syndrome
- Skin Reactions
- Other Malignancies
- Extravasation Injury
- Embryo-fetal Toxicity

6 ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Myelosuppression: Delay or reduce dose. Restart treatment based on ANC and platelet count recovery. (2.2) Complications of myelosuppression may lead to death. (5.1)
- Infections: Monitor for fever and other signs of infection or reactivation of infections and treat promptly. (5.2)
- Anaphylaxis and Infusion Reactions: Severe and anaphylactic reactions have occurred; monitor clinically and discontinue TREANDA. Pre-medicate in subsequent cycles for milder reactions. (5.3)
- Tumor Lysis Syndrome: Acute renal failure and death; anticipate and use supportive measures. (5.4)
- Skin Reactions: Discontinue for severe skin reactions. Cases of SJS and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. (5.5)
- Other Malignancies: Pre-malignant and malignant diseases have been reported. (5.6)
- Extravasation Injury: Assure good venous access and monitor infusion site during and after administration. (5.7)
- Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving TREANDA. (5.8, 8.1)

ADVERSE REACTIONS

- Most common non-hematologic adverse reactions for CLL (frequency \geq 15%) are pyrexia, nausea, and vomiting. (6.1)
- Most common non-hematologic adverse reactions for NHL (frequency \geq 15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. (6.1)
- Most common hematologic abnormalities for both indications (frequency \geq 15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-800-896-5855 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant CYP1A2 inducers or inhibitors have the potential to affect the exposure of bendamustine. (7)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Do not use if CrCL is $<$ 40 mL/min. Use with caution in lesser degrees of renal impairment. (8.6)
- Hepatic Impairment: Do not use in moderate or severe hepatic impairment. Use with caution in mild hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2015

- Pediatric Use
- Geriatric Use
- Renal Impairment
- Hepatic Impairment
- Effect of Gender

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- Chronic Lymphocytic Leukemia (CLL)
- Non-Hodgkin Lymphoma (NHL)

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- Safe Handling and Disposal
- How Supplied
- Storage

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

TREANDA® is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.

1.2 Non-Hodgkin Lymphoma (NHL)

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

2 DOSAGE AND ADMINISTRATION

2.1 Selection of TREANDA Formulation to Administer

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

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

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

TREANDA Injection and the reconstituted TREANDA for Injection have different concentrations of bendamustine hydrochloride. The concentration of bendamustine hydrochloride in the solution is 90 mg/mL and the concentration of bendamustine hydrochloride in the reconstituted solution of lyophilized powder is 5 mg/mL. **Do not mix or combine the two formulations.**

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

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

2.2 Dosing Instructions for CLL

Recommended Dosage:

The recommended dose is 100 mg/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:

TREANDA administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant \geq Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to \leq Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) $\geq 1 \times 10^9/L$, platelets $\geq 75 \times 10^9/L$], TREANDA can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. [see Warnings and Precautions (5.1)]

Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/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.

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

2.3 Dosing Instructions for NHL

Recommended Dosage:

The recommended dose is 120 mg/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:

TREANDA administration should be delayed in the event of a Grade 4 hematologic toxicity or clinically significant \geq Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to \leq Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) $\geq 1 \times 10^9/L$, platelets $\geq 75 \times 10^9/L$], TREANDA can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. [see Warnings and Precautions (5.1)]

Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/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.

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

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

- **If using a syringe to withdraw and transfer TREANDA Injection from the vial into the infusion bag, only use a polypropylene syringe with a metal needle and a polypropylene hub to withdraw and transfer TREANDA Injection into the infusion bag.**
- Each vial of TREANDA Injection is intended for single dose only.
- Aseptically withdraw the volume needed for the required dose from the 90 mg/mL solution using a polypropylene syringe with a metal needle and a polypropylene hub.
- Immediately transfer the solution to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 – 0.7 mg/mL.
- **After dilution of TREANDA Injection into the infusion bag, devices that contain polycarbonate or ABS, including infusion sets, may be used.**
- Visually inspect the filled syringe and the prepared infusion bag to ensure the lack of visible particulate matter prior to administration. The admixture should be a clear colorless to yellow solution.

Use either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible.

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

If a closed system transfer device or adapter that contains polycarbonate or ABS is to be used as supplemental protection during preparation¹, only use TREANDA for Injection, the lyophilized formulation.

- Each vial of TREANDA for Injection is intended for single dose only.
- Aseptically reconstitute each TREANDA for Injection vial as follows:
 - 25 mg TREANDA for Injection vial: Add 5 mL of only Sterile Water for Injection, USP.
 - 100 mg TREANDA for Injection vial: Add 20 mL of only Sterile Water for Injection, USP.
- Shake well to yield a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. If particulate matter is observed, the reconstituted product should not be used.
- Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 – 0.6 mg/mL. After transferring, thoroughly mix the contents of the infusion bag.
- Visually inspect the filled syringe and the prepared infusion bag to ensure the lack of visible particulate matter prior to administration. The admixture should be a clear and colorless to slightly yellow solution.

Use Sterile Water for Injection, USP, for reconstitution and then either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible.

General Information

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Any unused solution should be discarded according to institutional procedures for antineoplastics.

2.5 Admixture Stability

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

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

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored under refrigerated conditions at 2–8°C (36–46°F) or for 2 hours when stored at room temperature (15° to 30°C or 59° to 86°F) and room light. Administration of diluted TREANDA Injection must be completed within this period.

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

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored under refrigerated conditions at 2–8°C (36° to 46°F) or for 3 hours when stored at room temperature (15° to 30°C or 59° to 86°F) and room light. Administration of reconstituted and diluted TREANDA for Injection must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

TREANDA caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV). In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be $\geq 1 \times 10^9/L$ and the platelet count should be $\geq 75 \times 10^9/L$. [see Dosage and Administration (2.2) and (2.3)]

5.2 Infections

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

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

5.3 Anaphylaxis and Infusion Reactions

Infusion reactions to TREANDA have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experience Grade 3 or worse allergic-type reactions should not be rechallenged. Consider measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids in subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions. Discontinue TREANDA for patients with Grade 4 infusion reactions. Consider discontinuation for Grade 3 infusion reactions as clinically appropriate considering individual benefits, risks, and supportive care.

5.4 Tumor Lysis Syndrome

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

5.5 Skin Reactions

Skin reactions have been reported with TREANDA treatment in clinical trials and postmarketing safety reports, including rash, toxic skin reactions and bullous exanthema. Some events occurred when TREANDA was given in combination with other anticancer agents.

In a study of TREANDA (90 mg/m²) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert). Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to TREANDA cannot be determined.

Where skin reactions occur, they may be progressive and increase in severity with further treatment. Monitor patients with skin reactions closely. If skin reactions are severe or progressive, withhold or discontinue TREANDA.

5.6 Other Malignancies

There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with TREANDA, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with TREANDA therapy has not been determined.

5.7 Extravasation Injury

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

5.8 Embryo-fetal Toxicity

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

6 ADVERSE REACTIONS

The following serious adverse reactions have been associated with TREANDA in clinical trials and are discussed in greater detail in other sections of the label.

- Myelosuppression [see Warnings and Precautions (5.1)]
- Infections [see Warnings and Precautions (5.2)]
- Anaphylaxis and Infusion Reactions [see Warnings and Precautions (5.3)]
- Tumor Lysis Syndrome [see Warnings and Precautions (5.4)]
- Skin Reactions [see Warnings and Precautions (5.5)]
- Other Malignancies [see Warnings and Precautions (5.6)]
- Extravasation Injury [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Chronic Lymphocytic Leukemia

The data described below reflect exposure to TREANDA in 153 patients with CLL studied in an active-controlled, randomized trial. The population was 45-77 years of age, 63% male, 100% white, and were treatment naïve. All patients started the study at a dose of 100 mg/m² intravenously over 30 minutes on Days 1 and 2 every 28 days.

Adverse reactions were reported according to NCI CTC v.2.0. Non-hematologic adverse reactions (any grade) in the TREANDA group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%).

Other adverse reactions seen frequently in one or more studies included asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis.

Worsening hypertension was reported in 4 patients treated with TREANDA in the CLL trial and in none treated with chlorambucil. Three of these 4 adverse reactions were described as a hypertensive crisis and were managed with oral medications and resolved.

The most frequent adverse reactions leading to study withdrawal for patients receiving TREANDA were hypersensitivity (2%) and pyrexia (1%).

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in $\geq 5\%$ 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

| System organ class Preferred term | Number (%) of patients | | | |
|--|------------------------|----------------|-------------------------|----------------|
| | TREANDA (N=153) | | Chlorambucil (N=143) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Total number of patients with at least 1 adverse reaction | 121 (79) | 52 (34) | 96 (67) | 25 (17) |
| Gastrointestinal disorders | | | | |
| Nausea | 31 (20) | 1 (<1) | 21 (15) | 1 (<1) |
| Vomiting | 24 (16) | 1 (<1) | 9 (6) | 0 |
| Diarrhea | 14 (9) | 2 (1) | 5 (3) | 0 |
| General disorders and administration site conditions | | | | |
| Pyrexia | 36 (24) | 6 (4) | 8 (6) | 2 (1) |
| Fatigue | 14 (9) | 2 (1) | 8 (6) | 0 |
| Asthenia | 13 (8) | 0 | 6 (4) | 0 |
| Chills | 9 (6) | 0 | 1 (<1) | 0 |
| Immune system disorders | | | | |
| Hypersensitivity | 7 (5) | 2 (1) | 3 (2) | 0 |
| Infections and infestations | | | | |
| Nasopharyngitis | 10 (7) | 0 | 12 (8) | 0 |
| Infection | 9 (6) | 3 (2) | 1 (<1) | 1 (<1) |
| Herpes simplex | 5 (3) | 0 | 7 (5) | 0 |
| Investigations | | | | |
| Weight decreased | 11 (7) | 0 | 5 (3) | 0 |
| Metabolism and nutrition disorders | | | | |
| Hyperuricemia | 11 (7) | 3 (2) | 2 (1) | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Cough | 6 (4) | 1 (<1) | 7 (5) | 1 (<1) |
| Skin and subcutaneous tissue disorders | | | | |
| Rash | 12 (8) | 4 (3) | 7 (5) | 3 (2) |
| Pruritus | 8 (5) | 0 | 2 (1) | 0 |

The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2. These findings confirm the myelosuppressive effects seen in patients treated with TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

TREANDA® (bendamustine hydrochloride) Injection
TREANDA® (bendamustine hydrochloride) for Injection

TREANDA® (bendamustine hydrochloride) Injection
TREANDA® (bendamustine hydrochloride) for Injection

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

| Laboratory Abnormality | TREANDA N=150 | | Chlorambucil N=141 | |
|------------------------|---------------------|--------------------|-----------------------|--------------------|
| | All Grades n (%) | Grade 3/4 n (%) | All Grades n (%) | Grade 3/4 n (%) |
| Hemoglobin Decreased | 134 (89) | 20 (13) | 115 (82) | 12 (9) |
| Platelets Decreased | 116 (77) | 16 (11) | 110 (78) | 14 (10) |
| Leukocytes Decreased | 92 (61) | 42 (28) | 26 (18) | 4 (3) |
| Lymphocytes Decreased | 102 (68) | 70 (47) | 27 (19) | 6 (4) |
| Neutrophils Decreased | 113 (75) | 65 (43) | 86 (61) | 30 (21) |

In the CLL trial, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of Grade 3 or 4 were limited to 1% and 3% of patients, respectively. Patients treated with TREANDA may also have changes in their creatinine levels. If abnormalities are detected, monitoring of these parameters should be continued to ensure that further deterioration does not occur.

Non-Hodgkin Lymphoma

The data described below reflect exposure to TREANDA in 176 patients with indolent B-cell NHL treated in two single-arm studies. The population was 31-84 years of age, 60% male, and 40% female. The race distribution was 89% White, 7% Black, 3% Hispanic, 1% other, and <1% Asian. These patients received TREANDA at a dose of 120 mg/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 by System Organ Class and Preferred Term (N=176)

| System organ class Preferred term | Number (%) of patients* | |
|--|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| Total number of patients with at least 1 adverse reaction | 176 (100) | 94 (53) |
| Cardiac disorders | | |
| Tachycardia | 13 (7) | 0 |
| Gastrointestinal disorders | | |
| Nausea | 132 (75) | 7 (4) |
| Vomiting | 71 (40) | 5 (3) |
| Diarrhea | 65 (37) | 6 (3) |
| Constipation | 51 (29) | 1 (<1) |
| Stomatitis | 27 (15) | 1 (<1) |
| Abdominal pain | 22 (13) | 2 (1) |
| Dyspepsia | 20 (11) | 0 |
| Gastroesophageal reflux disease | 18 (10) | 0 |
| Dry mouth | 15 (9) | 1 (<1) |
| Abdominal pain upper | 8 (5) | 0 |
| Abdominal distension | 8 (5) | 0 |
| General disorders and administration site conditions | | |
| Fatigue | 101 (57) | 19 (11) |
| Pyrexia | 59 (34) | 3 (2) |
| Chills | 24 (14) | 0 |
| Edema peripheral | 23 (13) | 1 (<1) |
| Asthenia | 19 (11) | 4 (2) |
| Chest pain | 11 (6) | 1 (<1) |
| Infusion site pain | 11 (6) | 0 |
| Pain | 10 (6) | 0 |
| Catheter site pain | 8 (5) | 0 |
| Infections and infestations | | |
| Herpes zoster | 18 (10) | 5 (3) |
| Upper respiratory tract infection | 18 (10) | 0 |
| Urinary tract infection | 17 (10) | 4 (2) |
| Sinusitis | 15 (9) | 0 |
| Pneumonia | 14 (8) | 9 (5) |
| Febrile neutropenia | 11 (6) | 11 (6) |
| Oral candidiasis | 11 (6) | 2 (1) |
| Nasopharyngitis | 11 (6) | 0 |
| Investigations | | |
| Weight decreased | 31 (18) | 3 (2) |
| Metabolism and nutrition disorders | | |
| Anorexia | 40 (23) | 3 (2) |
| Dehydration | 24 (14) | 8 (5) |

| System organ class Preferred term | Number (%) of patients* | |
|--|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| Musculoskeletal and connective tissue disorders | | |
| Back pain | 25 (14) | 5 (3) |
| Arthralgia | 11 (6) | 0 |
| Pain in extremity | 8 (5) | 2 (1) |
| Bone pain | 8 (5) | 0 |
| Nervous system disorders | | |
| Headache | 36 (21) | 0 |
| Dizziness | 25 (14) | 0 |
| Dysgeusia | 13 (7) | 0 |
| Psychiatric disorders | | |
| Insomnia | 23 (13) | 0 |
| Anxiety | 14 (8) | 1 (<1) |
| Depression | 10 (6) | 0 |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | 38 (22) | 1 (<1) |
| Dyspnea | 28 (16) | 3 (2) |
| Pharyngolaryngeal pain | 14 (8) | 1 (<1) |
| Wheezing | 8 (5) | 0 |
| Nasal congestion | 8 (5) | 0 |
| Skin and subcutaneous tissue disorders | | |
| Rash | 28 (16) | 1 (<1) |
| Pruritus | 11 (6) | 0 |
| Dry skin | 9 (5) | 0 |
| Night sweats | 9 (5) | 0 |
| Hyperhidrosis | 8 (5) | 0 |
| Vascular disorders | | |
| Hypotension | 10 (6) | 2 (1) |

*Patients may have reported more than 1 adverse reaction.

NOTE: Patients counted only once in each preferred term category and once in each system organ class category.

Hematologic toxicities, based on laboratory values and CTC grade, in NHL patients treated in both single arm studies combined are described in Table 4. Clinically important chemistry laboratory values that were new or worsened from baseline and occurred in >1% of patients at Grade 3 or 4, in NHL patients treated in both single arm studies combined were hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).

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

| Hematology variable | Percent of patients | |
|-----------------------|---------------------|-----------|
| | All Grades | Grade 3/4 |
| Lymphocytes Decreased | 99 | 94 |
| Leukocytes Decreased | 94 | 56 |
| Hemoglobin Decreased | 88 | 11 |
| Neutrophils Decreased | 86 | 60 |
| Platelets Decreased | 86 | 25 |

In both studies, serious adverse reactions, regardless of causality, were reported in 37% of patients receiving TREANDA. The most common serious adverse reactions occurring in ≥5% of patients were febrile neutropenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or postmarketing experience were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome.

Serious drug-related adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumor lysis syndrome and infusion reactions (*see Warnings and Precautions (5)*). Adverse reactions occurring less frequently but possibly related to TREANDA treatment were hemolysis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and skin necrosis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TREANDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic systems disorders: Pancytopenia

Cardiovascular disorders: Atrial fibrillation, congestive heart failure (some fatal), myocardial infarction (some fatal), palpitation

General disorders and administration site conditions: Injection site reactions (including phlebitis, pruritus, irritation, pain, swelling), infusion site reactions (including phlebitis, pruritus, irritation, pain, swelling)

Immune system disorders: Anaphylaxis

Infections and infestations: Pneumocystis jiroveci pneumonia.

Respiratory, thoracic and mediastinal disorders: Pneumonitis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (with concomitant)

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