CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-249/S-1

Trade Name:	Treanda
Generic or Proper Name:	bendamustine hydrochloride, for Injection, 100 mg
Sponsor:	Cephalon, Inc.
Approval Date:	May 1, 2009
Indication:	provides for the addition of a new 25 mg vial

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 22-249/S-1

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249/S-1

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-249/S-001

Cephalon, Inc.
Attention: Carol S. Marchione
Senior Director and Group Leader
41 Moores Road
Frazer, PA 19355

Dear Ms. Marchione:

Please refer to your supplemental new drug application dated August 27, 2008, received August 28, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Treanda® (bendamustine hydrochloride) for Injection, 100 mg.

We acknowledge receipt of your submissions dated August 27, 2008 and November 19, 2008.

This supplemental new drug application provides for the addition of a 25 mg vial for the use of Treanda® (bendamustine hydrochloride) for Injection for the treatment of patients with Chronic Lymphocytic Leukemia and for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-249/S-001."

We remind you of your outstanding postmarketing study commitments listed in the March 20, 2008, approval letter. These commitments are listed below.

1. Cephalon commits to providing an updated study report of Protocol 02CLLIII titled *"Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naive Patients with (Binet Stage B/C) BCLL Requiring Therapy"* at data cut off date in May 2008. Response rate, progression-free survival, overall survival and safety updates will be provided in this study report.

Protocol Submission: N/A
Study Start: N/A
Final Report Submission: February 28, 2009

2. Cephalon commits to submitting the results and data from the ADME Study 1039 titled "An Open-Label Study to Investigate the Pharmacokinetics (Distribution, Metabolism, and Excretion) of Bendamustine Hydrochloride Following Intravenous Infusion of [$_{14}$C]Bendamustine Hydrochloride in Patients With Relapsed or Refractory Malignancy (Hematologic or Nonhematologic)". Results from this study may indicate a need for dedicated renal and/or hepatic organ impairment studies.

   Protocol Submission: May 31, 2008
   Study Start: December 31, 2008
   Final Report Submission: March 31, 2010

3. Cephalon commits to conducting a study to assess the potential for bendamustine to prolong the QT interval in patients. The QT plan will be submitted prior to initiation for IRT review and concurrence.

   Protocol Submission: July 31, 2008
   Study Start: December 31, 2008
   Final Report Submission: June 30, 2010

4. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of fluvoxamine (CYP1A2 inhibitor) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

   Protocol Submission: March 31, 2010
   Study Start: September 30, 2010
   Final Report Submission: July 31, 2012

5. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of smoking (CYP1A2 inducer) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

   Protocol Submission: March 31, 2010
   Study Start: September 30, 2010
   Final Report Submission: December 31, 2012

6. Cephalon commits to conducting *in vitro* screens to determine if bendamustine is a p-glycoprotein substrate or inhibitor.

   Protocol Submission: March 31, 2008
   Study Start: September 30, 2007
   Final Report Submission: June 30, 2008

7. Cephalon commits to assess the physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: D5W, lactated Ringers and half normal saline (0.45% sodium chloride).

   Protocol submission: April 1, 2008
   Study start: May 15, 2008
   Final Report: September 1, 2008

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Drug Oncology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Milinda Vialpando, Regulatory Project Manager, at (301) 796-1444.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amna Ibrahim
5/1/2009 01:01:36 PM
For Dr Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249/S-1

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TREANDA® (bendamustine hydrochloride) for Injection, for intravenous infusion

Initial U.S. Approval: 2008

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

Indications and Usage, Non-Hodgkin's Lymphoma (NHL) (1.2)	10/2008
Dosage and Administration, Dosing Instructions for NHL (2.2)	10/2008
Dosage and Administration, Reconstitution/Preparation for Intravenous Administration (2.4)	11/2008
Dosage and Administration, Admixture Stability (2.5)	10/2008
Warnings and Precautions, Myelosuppression (5.1)	10/2008
Warnings and Precautions, Skin Reactions (5.5)	10/2008
Warnings and Precautions, Other Malignancies (5.6)	10/2008

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

TREANDA for Injection is an alkylating drug indicated for treatment of patients with:

- Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. (1.1)
- Indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. (1.2)

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

For CLL:

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

For NHL:

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

General Dosing Considerations:

- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity (2.1, 2.2)
- TREANDA for Injection must be reconstituted and further diluted prior to infusion. (2.4)

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

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

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

Known hypersensitivity to bendamustine or mannitol (4)

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

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

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

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

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

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

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

----------DRUG INTERACTIONS----------

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

----------USE IN SPECIFIC POPULATIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

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

1.2 Non-Hodgkin's Lymphoma (NHL)

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions for CLL

Recommended Dosage:

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

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

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

Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle.

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

2.2 Dosing Instructions for NHL

Recommended Dosage:

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

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

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

Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

2.3 General Considerations for Tumor Lysis Syndrome

Consider using allopurinol as prevention for patients at high risk of tumor lysis syndrome for the first few weeks of treatment.

2.4 Reconstitution/Preparation for Intravenous Administration

- Aseptically reconstitute each TREANDA vial as follows:
  - 25 mg TREANDA vial: Add 5mL of only **Sterile Water for Injection, USP.**
  - 100 mg TREANDA vial: Add 20 mL of only **Sterile Water for Injection, USP**.

  Shake well to yield a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. If particulate matter is observed, the reconstituted product should not be used.

- Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 – 0.6 mg/mL. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colorless to slightly yellow solution.

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

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

2.5 Admixture Stability

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

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8 C or 36-47 F) or for 3 hours when stored at room temperature (15-30 C or 59-86 F) and room light. Administration of TREANDA must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Patients treated with TREANDA are likely to experience myelosuppression. In the two NHL studies, 98% of patients had Grade 3-4 myelosuppression (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils closely. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Hematologic nadirs may

require dose delays if recovery to the recommended values have not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be $\geq 1 \times 10^9$/L and the platelet count should be $\geq 75 \times 10^9$/L. *[See Dosage and Administration (2.1) and (2.2)]*

5.2 Infections

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

5.3 Infusion Reactions and Anaphylaxis

Infusion reactions to TREANDA have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome associated with TREANDA treatment has been reported in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, close monitoring of blood chemistry, particularly potassium and uric acid levels, and the use of allopurinol during the first few weeks of TREANDA therapy in patients at high risk.

5.5 Skin Reactions

A number of skin reactions have been reported in clinical trials and post-marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when TREANDA was given in combination with other anticancer agents, so the precise relationship to TREANDA is uncertain. In a study of TREANDA (90 mg/m^2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert). The relationship to TREANDA cannot be determined. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are severe or progressive, TREANDA should be withheld or discontinued.

5.6 Other Malignancies

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

5.7 Use in Pregnancy

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

6 ADVERSE REACTIONS

The data described below reflect exposure to TREANDA in 349 patients who participated in an actively-controlled trial (N=153) for the treatment of CLL and two single-arm studies (N=176) for the treatment of indolent B-cell NHL. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

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

6.1 Clinical Trials Experience in CLL

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

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

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

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

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

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

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

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

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

	TREANDA N=150		Chlorambucil N=141	
Laboratory Abnormality	**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 randomized CLL clinical study, 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 significant deterioration does not occur.

6.2 Clinical Trials Experience in NHL

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/m^2 intravenously on Days 1 and 2 for up to 8 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)
Decreased appetite	22 (13)	1 (<1)
Hypokalemia	15 (9)	9 (5)
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	Grades 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 post-marketing 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.

6.3 Post-Marketing 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: anaphylaxis; and injection or infusion site reactions including pruritus, irritation, pain, and swelling.

7 DRUG INTERACTIONS

No formal clinical assessments of pharmacokinetic drug-drug interactions between TREANDA and other drugs have been conducted.

Bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

The role of active transport systems in bendamustine distribution has not been fully evaluated. *In vitro* data suggest that P-glycoprotein, breast cancer resistance protein (BCRP), and/or other efflux transporters may have a role in bendamustine transport.

Based on *in vitro* data, bendamustine is not likely to inhibit metabolism via human CYP isoenzymes CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5, or to induce metabolism of substrates of cytochrome P450 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[See Warnings and Precautions (5.7)]*

TREANDA can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine from 210 mg/m^2 (70 mg/kg) in mice administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (exencephaly, cleft palates, 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 dosing in mice on gestation days 7-11 resulted in an increase in resorptions from 75 mg/m^2 (25 mg/kg) and an increase in abnormalities from 112.5 mg/m^2 (37.5 mg/kg) similar to those seen after a single intraperitoneal administration. Single intraperitoneal doses of bendamustine from 120 mg/m^2 (20 mg/kg) in rats administered on gestation days 4, 7, 9, 11, or 13 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. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for bendamustine in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of TREANDA in pediatric patients have not been established.

8.5 Geriatric Use

In CLL and NHL studies, there were no clinically significant differences in the adverse reaction profile between geriatric (≥ 65 years of age) and younger patients.

Chronic Lymphocytic Leukemia

In the randomized CLL clinical study, 153 patients received TREANDA. The overall response rate for patients younger than 65 years of age was 70% (n=82) for TREANDA and 30% (n=69) for chlorambucil. The overall response rate for patients 65 years or older was 47% (n=71) for TREANDA and 22% (n=79) for chlorambucil. In patients younger than 65 years of age, the median progression-free survival was 19 months in the TREANDA group and 8 months in the chlorambucil group. In patients 65 years or older, the median progression-free survival was 12 months in the TREANDA group and 8 months in the chlorambucil group.

Non-Hodgkin's Lymphoma

Efficacy (Overall Response Rate and Duration of Response) was similar in patients < 65 years of age and patients ≥ 65 years. Irrespective of age, all of the 176 patients experienced at least one adverse reaction.

8.6 Renal Impairment

No formal studies assessing the impact of renal impairment on the pharmacokinetics of bendamustine have been conducted. TREANDA should be used with caution in patients with mild or moderate renal impairment. TREANDA should not be used in patients with CrCL < 40 mL/min. *[See Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

No formal studies assessing the impact of hepatic impairment on the pharmacokinetics of bendamustine have been conducted. TREANDA should be used with caution in patients with mild hepatic impairment. TREANDA should not be used in patients with moderate (AST or ALT 2.5-10 X ULN and total bilirubin 1.5-3 X ULN) or severe (total bilirubin > 3 X ULN) hepatic impairment. *[See Clinical Pharmacology (12.3)]*

8.8 Effect of Gender

No clinically significant differences between genders were seen in the overall incidences of adverse reactions in either CLL or NHL studies.

Chronic Lymphocytic Leukemia

In the randomized CLL clinical study, the overall response rate (ORR) for men (n=97) and women (n=56) in the TREANDA group was 60% and 57%, respectively. The ORR for men (n=90) and women (n=58) in the chlorambucil group was 24% and 28%, respectively. In this study, the median progression-free survival for men was 19 months in the TREANDA treatment group and 6 months in the chlorambucil treatment group. For women, the median progression-free survival was 13 months in the TREANDA treatment group and 8 months in the chlorambucil treatment group.

Non-Hodgkin's Lymphoma

The pharmacokinetics of bendamustine were similar in male and female patients with indolent NHL. No clinically-relevant differences between genders were seen in efficacy (ORR and DR).

10 OVERDOSAGE

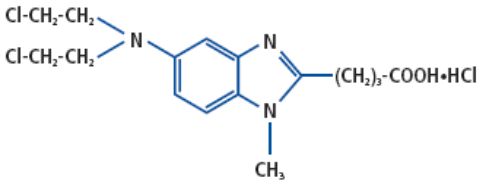
The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

Across all clinical experience, the reported maximum single dose received was 280 mg/m^2. 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), sinus 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 overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

11 DESCRIPTION

TREANDA contains bendamustine hydrochloride, an alkylating drug, as the active ingredient. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$, and the molecular weight is 394.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:



TREANDA (bendamustine hydrochloride) for Injection is intended for intravenous infusion only after reconstitution with Sterile Water for Injection, USP, and after further dilution with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. It is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single-use 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.

12.3 Pharmacokinetics

Absorption

Following a single IV dose of bendamustine hydrochloride C_{max} typically occurred at the end of infusion. The dose proportionality of bendamustine has not been studied.

Distribution

In vitro, the binding of bendamustine to human serum plasma proteins ranged from 94-96% and was concentration independent from 1-50 µg/mL. Data suggest that bendamustine is not likely to displace or to be displaced by highly protein-bound drugs. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 µg/mL indicating that bendamustine distributes freely in human red blood cells. In humans, the mean steady state volume of distribution (V_{ss}) was approximately 25 L.

Metabolism

In vitro data indicate that bendamustine is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. *In vitro*, studies indicate that two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are 1/10 and 1/100 that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to bendamustine.

In vitro studies using human liver microsomes indicate that bendamustine does not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 enzymes in primary cultures of human hepatocytes.

Elimination

No mass balance study has been undertaken in humans. Preclinical radiolabeled bendamustine studies showed that approximately 90% of drug administered was recovered in excreta primarily in the feces.

Bendamustine clearance in humans is approximately 700 mL/minute. After a single dose of 120 mg/m^2 bendamustine IV over 1-hour the intermediate $t_{½}$ of the parent compound is approximately 40 minutes. The mean apparent terminal elimination $t_{½}$ of M3 and M4 are approximately 3 hours and 30 minutes respectively. Little or no accumulation in plasma is expected for bendamustine administered on Days 1 and 2 of a 28-day cycle.

Renal Impairment

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of renal impairment (CrCL 40 - 80 mL/min, N=31) on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with CrCL < 40 mL/min.

These results are however limited, and therefore bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < 40 mL/min. *[See Use in Specific Populations (8.6)]*

Hepatic Impairment

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of mild (total bilirubin ≤ ULN, AST ≥ ULN to 2.5 x ULN, and/or ALP ≥ ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment.

These results are however limited, and therefore bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5 - 10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment. *[See Use in Specific Populations (8.7)]*

Effect of Age

Bendamustine exposure (as measured by AUC and C_{max}) has been studied in patients ages 31 through 84 years. The pharmacokinetics of bendamustine (AUC and C_{max}) were not significantly different between patients less than or greater than/equal to 65 years of age. *[See Use in Specific Populations (8.4, 8.5)]*

Effect of Gender

The pharmacokinetics of bendamustine were similar in male and female patients. *[See Use in Specific Populations (8.8)]*

Effect of Race

The effect of race on the safety, and/or efficacy of TREANDA has not been established. Based on a cross-study comparison, Japanese subjects (n = 6) had on average exposures that were 40% higher than non-Japanese subjects receiving the same dose. The significance of this difference on the safety and efficacy of TREANDA in Japanese subjects has not been established.

12.4 Pharmacokinetics/Pharmacodynamics

Based on the pharmacokinetics/pharmacodynamics analyses of data from NHL patients, a correlation was observed between nausea and bendamustine C_{max}.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bendamustine was carcinogenic in mice. After intraperitoneal injections at 37.5 mg/m^2/day (12.5 mg/kg/day, the lowest dose tested) and 75 mg/m^2/day (25 mg/kg/day) for four days, peritoneal sarcomas in female AB/jena mice were produced. Oral administration at 187.5 mg/m^2/day (62.5 mg/kg/day, the only dose tested) for four days induced mammary carcinomas and pulmonary adenomas.

Bendamustine is a mutagen and clastogen. In a reverse bacterial 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/m^2, the lowest dose tested.

Impaired spermatogenesis, azoospermia, and total germinal aplasia have been reported in male patients treated with alkylating agents, especially in combination with other drugs. In some instances spermatogenesis may return in patients in remission, but this may occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacities.

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, 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), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean 65.7x10^9/L vs. 65.1x10^9/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 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/m^2, 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[1].

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

	TREANDA (N=153)	Chlorambucil (N=148)	p-value
Response Rate n(%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95% CI)	(51.0, 66.6)	(18.6, 32.7)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)**	4 (3)	0	
Partial response (PR)†	73 (48)	37 (25)	
Progression-Free Survival††			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		<0.0001

CI = confidence interval

* CR was defined as peripheral lymphocyte count ≤ 4.0 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin > 110g/L, without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days.

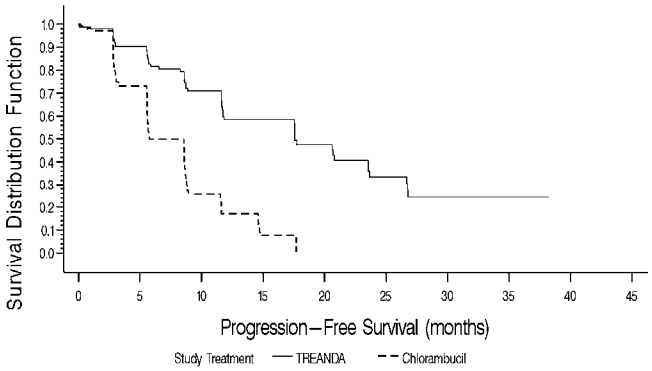
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

† PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/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.

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's 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/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 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 unconfirmed + partial response) and duration of response (DR) as summarized in Table 6.

Table 6: Efficacy Data for NHL*

	TREANDA (N=100)
Response Rate (%)	
Overall response rate (CR+CRu+PR)	74
(95% CI)	(64 3, 82.3)
Complete response (CR)	13
Complete response unconfirmed (CRu)	4
Partial response (PR)	57
Duration of Response (DR)	
Median, months (95% CI)	9.2 months (7 1, 10.8)

CI = confidence interval

*IRC assessment was based on modified International Working Group response criteria (IWG-RC)[2]. 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

1. Cheson et al. National Cancer Institute –sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia. Blood Vol 87 1996:pp 4990.

2. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. *J Clin Oncol.* 1999;17:1244-1253.

3. Preventing occupational exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

4. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.

5. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm*. 2006; 63:1172-1193.

6. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from TREANDA. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of TREANDA contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published[3-6]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

16.2 How Supplied

TREANDA (bendamustine hydrochloride) for Injection is supplied in individual cartons as follows:

NDC 63459-390-08 TREANDA (bendamustine hydrochloride) for Injection, 25 mg in 8 mL amber single-use vial

NDC 63459-391-20 TREANDA (bendamustine hydrochloride) for Injection, 100 mg in 20 mL amber single-use vial

16.3 Storage

TREANDA 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
  Patients should be informed of the possibility of mild or serious allergic reactions and to immediately report rash, facial swelling, or difficulty breathing during or soon after infusion.

- Myelosuppression
  Patients should be informed of the likelihood that TREANDA will cause a decrease in white blood cells, platelets, and red blood cells. They will need frequent monitoring of these parameters. They should be instructed to report shortness of breath, significant fatigue, bleeding, fever, or other signs of infection.

- Pregnancy and Nursing
  TREANDA can cause fetal harm. Women should be advised to avoid becoming pregnant throughout treatment and for 3 months after TREANDA therapy has stopped. Men receiving TREANDA should use reliable contraception for the same time period. Advise patients to report pregnancy immediately. Advise patients to avoid nursing while receiving TREANDA.

- 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.

- 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.

- Diarrhea
  Advise patients that TREANDA may cause diarrhea. Patients should report diarrhea to the physician so that symptomatic treatment may be provided.

- Rash
  Advise patients that a mild rash or itching may occur during treatment with TREANDA. Advise patients to immediately report severe or worsening rash or itching.

Manufactured by:
Pharmachemie B.V.
The Netherlands

Manufactured for:
Cephalon, Inc.
Frazer, PA 19355

TREANDA is a registered trademark of Cephalon, Inc.

Label Code: PI-40014-XX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249/S-1

CHEMISTRY REVIEW

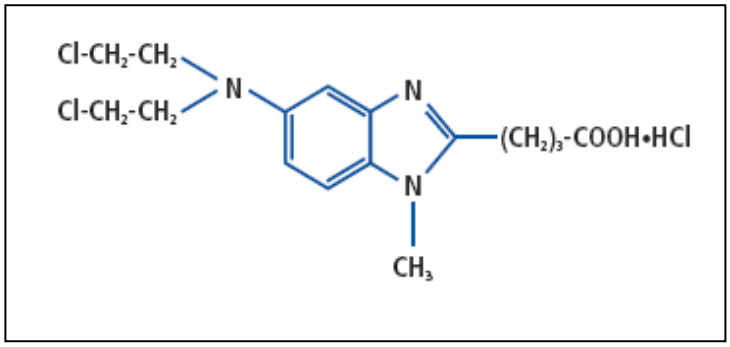
Chemist Review: # 1	**1. Division:** ONDQA Division IV, Branch VIII and HFD-150	2. **NDA Number** 22-249

3. Name and Address of Applicant: Cephalon, Inc. 41 Moores Road P. O. Box 4011 Frazer, PA 19355	**4. Supplement(s):** **Number:** SCF-001 (PAS), dated 8-27-08 **Date(s):** User Fee date is 12-27-08
5. Name of Drug: TREANDA® (bendamustine HCl) for injection	**6. Nonproprietary name:** Bendamustine for injection

7. Supplement Provides for the addition of a 25-mg vial; the currently-approved presentation is a 100-mg vial.	**8. Amendment(s):**

9. Pharmacological Category: Treatment of chronic lymphocytic leukemia	**10. How Dispensed:** Rx	**11. Related Documents:** NA
12. Dosage Form: Lyophilized powder for injection	**13. Potency:** 100 and **<u>25 mg</u>** bendamustine hydrochloride per vial	

14. Chemical Name and Structure: bendamustine•HCl, $C_{16}H_{21}Cl_2N_3O_2$•HCl, 394.7 g/mol



15. Comments: This prior-approval supplement (PAS) proposes the addition of a new strength dosage unit, namely a formulation providing 25 mg of bendamustine•HCl in a lyophilized powder contained in a 8-mL vial. This NDA currently has one approved dosage unit, consisting of a formulation providing 100 mg of bendamustine•HCl in a lyophilized powder in a 20-mL vial. The following is noted:

- The drug substance, bendamustine•HCl is unchanged from that, which was previously approved.
- There is no change to the composition of the drug product (b)(4)).
- There is no change to the manufacturing facility for the drug product (the currently approved facility, filling room, and equipment are used).
- There is no change to the drug product specifications and methods (with the exception of the description, which addresses the new [smaller] vial size).

The following CMC information has been changed, in support of the new dosage unit:

- The bulk solution for the 25-mg vials is manufactured (b)(4) (b)(4)
- There is a change to the fill (b)(4)
- The applicant provided a change in the (b)(4) process controls.
- The 25-mg dosage unit is filled into (b)(4) vials for the 100-mg dosage unit.

The revised (b)(4) process controls were consulted to the microbiology staff for review. The application is recommended for approval on the basis of sterility assurance (microbiology review dated 12-23-08, S. Langille, Ph.D.).

The applicant provided the following CMC information in support of the new dosage unit:

- Release and stability data from four (4) commercial-scale batches of drug product (25-mg lyophilized powder for injection)
- Drug product specifications for the 25-mg lyophilized powder
- Drawing and specifications for the new container closure system (8-mL glass vials)
- Integrity test data for the 8-mL vial
- Data to support the (b)(4) for the 25-mg lyophilized powder
- Updated manufacturing process and process parameters

The integrity test (b)(4) information were addressed in the consult microbiology review.

The applicant has also utilized this supplement to include revisions to the following sections per FDA requests made as conditions for approval of original NDA 22-249:

- Maximum hold time and temperature included in section 3.2.P.3.3
- Maximum hold time and bioburden limit for (b)(4) in section 3.2.P.3.4
- Revised specifications for the drug product in section 3.2.P.5.1

The evaluation of the manufacturing process and controls, the batch analytical data, and the stability data indicated that the new-strength product may be approved form the standpoint of CMC.

In support of the 25-mg vials, a revised package insert was provided.

16. Conclusions and Recommendations: Recommend approval from the standpoint of CMC.

17. Name: **David B. Lewis, Ph.D., Chemist**	**Signature:**	**Date: 12-23-08**
18. Concurrence: **Hasmukh Patel, Ph.D., Branch Chief** **ONDQA/DPME/Branch VIII**	**Signature:**	**Date:**

Chemistry Reviewer Notes:

This prior-approval supplement provides the addition of a new dosage unit (25-mg vial). The drug product is currently approved as a 100-mg vial. The drug product consists of a lyophilized powder for injection. The currently approved product provides 100 mg of bendamustine•HCl, when reconstituted with 20 mL of sterile water for injection (SWFI). *It is noted that the re-constituted product is further diluted in normal saline (0.9% NaCl) for injection into patients*. The 100-mg vial contains a lyophilized powder containing 100 mg of bendamustine•HCl in a 20-mL amber glass vial.

The proposed dosage unit contains a lyophilized powder containing 25 mg of bendamustine•HCl in a 8-mL amber glass vial, to be reconstituted by the addition of 5 mL SWFI. *Like the 100-mg vial, the reconstituted 25-mg vial is further diluted by addition to a NS injection and then administered to the patient*.

Notes: the following CMC information is unchanged (as related to the approved 100-mg TREANDA vials), and is provided to this supplement by reference to the approved NDA 22-249:

- All information regarding the drug substance, bendamustine•HCl is unchanged from that approved for this NDA.
- There is no change to the composition of the drug (b)(4) (b)(4) (b)(4) The ratio of (b)(4) and the concentrations (b)(4) in the (b)(4) are unchanged.
- The drug product will continue to be manufactured in the approved facility, using the (b)(4) manufacturing equipment (with the exception of (b)(4) (b)(4).
- All analytical methods and specifications for the drug product are unchanged.

The following CMC information is new (revised) for the lower-strength vial:

- A (b)(4) is used for manufacture of the 25-mg vials. This is addressed in the CMC review, and evaluated via batch analytical results and stability data.
- The (b)(4). This is evaluated in both the consult microbiology review, and in this (CMC) review.
- The process controls for the (b)(4) were changed. This issue was consulted to the microbiology staff for review. In addition, the effect of this change is evaluated in this review via assessment of in-use stability (reconstitution behavior/performance) and batch analytical results and stability data.
- The (b)(4). This is evaluated in the CMC review (container closure section, batch analytical results, and stability data). The new CCS also affects (b)(4) these issues are addressed within the microbiology review.

Note: The revised (b)(4) controls and other sterility assurance issues were consulted to the microbiology staff for review. *The application is recommended for approval on the basis of sterility assurance (microbiology review dated 12-23-08, S. Langille, Ph.D.)*.

The following CTD sections of NDA 22-249 are addressed in this review:

3.2.P.1, **DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT**:

A comparison of the composition of the approved and proposed dosage units were provided in Table 1, as follows:

Table 1: Composition of Drug Product

Component	Reference to Standard	Function	Amount per 25mg/Vial	Amount per 100mg/Vial
Bendamustine HCl	In house standard	Active Ingredient	25 mg	100 mg
Mannitol	USP			(b)(4)

Note: the ratio (b)(4) .

3.2.P.2, **PHARMACEUTICAL DEVELOPMENT**:

P.2.2, **DRUG PRODUCT**: The applicant is proposing to market a new vial presentation, designed to provide one-quarter (1/4) of the dose of the approved presentation. The (b)(4) (b)(4) formulation is unchanged, (b)(4) The feasibility of the lower-dose vial was supported as follows:

Reconstitution Information:

- Each vial of bendamustine•HCl for injection, 25 mg/vial is reconstituted with 5 mL of sterile water for injection (SWFI) to yield a solution equivalent to 5 mg of bendamustine•HCl per mL. **Note**: *the approved 100-mg/vial product is reconstituted with 20 mL of SWFI, yielding a solution of the same constitution*. The applicant evaluated the reconstituted 25-mg vial for injection by determining the *color of solution after reconstitution*, along with *reconstitution time* (information provided in Tables 3 and 4, PD section of supplement). This data supported the same recommended D&A (how-used) information as currently used for the 100-mg vials (with the exception of a smaller volume of SWFI for reconstitution).

P.2.3, **MANUFACTURING PROCESS DEVELOPMENT**:

- The applicant utilized the approved manufacturing process (b)(4) formulation for the smaller (25-mg) vials. The (b)(4) .

- The applicant provided the following maximum hold times for the formulated [redacted]
- The applicant qualified the currently approved [redacted] for use in the 25-mg vial formulation and process. As illustrated in Table 2, [redacted]
- *The [redacted] for the 25-mg vials was modified from that used for the 100-mg vials by* [redacted]

The [redacted] manufacture (including hold times) is unchanged from that approved for the manufacture of the 100-mg vials, and remains adequate from standpoint of CMC. The revised [redacted] was consulted to microbiology staff for review, and was found adequate regarding sterility assurance (Microbiology review dated 12-23-08, S. Langille, Ph.D., reviewer).

The [redacted] parameters for the 25-mg (and 100-mg) products are as follows:

[redacted]

P.2.4, **CONTAINER CLOSURE SYSTEM DEVELOPMENT**:

- The CCS for the 25-mg vials is an 8-cc (b)(4) amber tubing glass vial stoppered with 20-mm bromobutyl lyophilization stopper, and sealed with aluminum flip-off seals. The CCS is identical to that used for the 100-mg vials with the exception of SIZE and FLIP-OFF SEAL COLOR. (b)(4)

P.2.5, **MICROBIOLOGICAL ATTRIBUTES**:

- The 25-mg vials are sterile single-use vials without antimicrobials. The long-term stability data indicates that the vials remain sterile throughout the shelf life (as determined by USP sterility test). Further information regarding maintenance of sterility was provided as container closure integrity tests (b)(4) These studies (indicating that container closure integrity is maintained at all tested storage conditions) were addressed in the microbiology review, and found adequate.

P.2.6, **COMPATIBILITY**:

- The 25-mg vials are labeled for reconstitution in 5 mL SWFI (in the lyophilization vial). The stability of the reconstituted bendamustine•HCl solutions (in the primary 8-mL glass vials) was addressed as follows:
  - Vials were reconstituted per the labeled procedure and stored up to (b)(4) at (b)(4) with light and up to (b)(4) without light.
  - bendamustine•HCl was determined (assay) for the stored samples by HPLC; results were described as similar to those determined for the approved 100-mg vials (reconstituted in 20 mL SWFI in 20-mL vials).
  - The labeled in-use stability for the 25-mg vials is the same as that for the approved 100-mg vials (24 hours at 5ºC and 1 hour at 25ºC). In addition, the in-use stability of the diluted reconstituted solution (in IV infusion bags of normal saline) was the same as that for the 100-mg vials: 24 hours if refrigerated and 3 hours at room temperature when exposed to light. The compatibility of bendamustine•HCl for injection (25-mg vials) with plastic syringes, infusion sets, glass vials, and infusion bags was determined to be the same as that determined for the approved 100-mg vials.

Evaluation: *Adequate*. The pharmaceutical development section described the studies which determined the 25-mg vials to be suitably based on the approved 100-mg vials. Most attributes and processes are unchanged. All dosing information remains suitable for the new smaller vials.

P.3, **MANUFACTURE**:

- P.3.1, **MANUFACTURER**: unchanged. The currently approved manufacturing facility was utilized for the manufacture of the 25-mg vials; manufacture takes place in the same manufacturing (b)(4) used for the approved 100-mg vials.
- P.3.2, **BATCH FORMULA**: the batch formula for the 25-mg vials is basically the same as that for the 100-mg vials ((b)(4) as illustrated below:

(b)(4)

- P.3.3, **DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS**: The applicant provided a description of the facility and process, along with process equipment for use in manufacture of the 25-mg vials. A manufacturing process flow diagram was also provided. The following statements were made regarding comparison between the manufacture of the approved 100-mg vials and the proposed 25-mg vials:
  - (b)(4) .
  - (b)(4)
  - (b)(4)
  - (b)(4) .

Notes: The use (b)(4) . The use of a (b)(4) (b)(4) could potentially impact drug product quality, stability, and sterility. The issue of sterility assurance is addressed in the microbiology review (recommended APPROVAL). The

issue of drug product quality (25-mg vials) is addressed from the standpoint of CMC *via* evaluation of batch analytical data and stability data (later in this review). It is noted that during pharmaceutical development (section 3.2.P.2), the applicant demonstrated that the 25-mg vials for injection displayed similar reconstitution behavior/performance as the approved 100-mg vials for injection.

- P.3.4, CONTROLS OF CRITICAL STEPS AND INTERMEDIATES: The applicant provided the in-process controls for (b)(4) These controls are reproduced below:

Table 1: In-process Control and Tests

(b)(4)

(b)(4)

).

The in-process controls for the (b)(4) (approved 100-mg vials and proposed 25-mg vials) are provided in Table 2 (Section 3.2.P.3.4), and are reproduced below:

(b)(4)

Notes: The (b)(4)

- P.3.5, PROCESS VALIDATION: The applicant provided (b)(4) ls.
- The applicant did provide (b)(4) .
- The applicant provided validation data for the (b)(4) (b)(4) the 25-mg vials are identical to the stoppers used or the approved 100-mg vials.
- The applicant provided information to validate the holding periods (b)(4) are appropriate for the manufacture of the 25-mg vials, and are adequate from the standpoint of CMC.
- The applicant provided validation of (b)(4) . This information is referred to original NDA 22-249 for design of experiments and validation of the facility and general process. Table 3 (section 3.2.P.3.5) (b)(4) . According to this table, (b)(4)

no units that were determined to be contaminated. This study is also addressed in them microbiology review.

- The applicant qualified the (b)(4) .

- 3.2.P.5.1, **SPECIFICATIONS**: The applicant provided the specifications for the 25-mg vials in Table 1 (section P.5.1). These are reproduced below:

Table 1: Specification for Bendamustine HCl for Injection, 25 and 100 mg/vial

Test	Method	Acceptance Criteria
(b)(4)		

Notes: The specification for the 25-mg vials is the same as that approved for the 100-mg vials, since the assay is expressed as percent label claim. All analytical methods are identical. The specification may be considered to be adequate to control the 25-mg vials.

- 3.2.P.5.4, BATCH ANALYSES: The applicant provided batch analyses for the following (b)(4):

Table 1: Summary of Bendamustine HCl Batches Utilized for Stability Studies (25 mg/vial)

Lot number	Stability protocol number	Drug substance lot number
A425363	(b)(4)	
A434749		
A434750		
A434751		

Results for exhibit batches:

Table 2: Batch Analysis for Bendamustine HCl Vials, Lots A425363, A434749, A434750, and A434751

Lot number	A425363	A434749	A434750	A434751
				(b)(4)

Table 2: Batch Analysis for Bendamustine HCl Vials, Lots A425363, A434749, A434750, and A434751 (continued)

Lot number	A425363	A434749	A434750	A434751
				(b)(4)

Table 2: Batch Analysis for Bendamustine HCl Vials, Lots A425363, A434749, A434750, and A434751 (continued)

Lot number	A425363	A434749	A434750	A434751
				(b)(4)

Evaluation: *Adequate.* (b)(4) batches met all specifications at release. The quantitative attributes appeared to be consistent between the four batches (b)(4) The analytical results for the exhibit batches indicated that the quality of the manufactured 25-mg vials was acceptable.

- 3.2.P.7, CONTAINER CLOSURE SYSTEM: The 25-mg vials (bendamustine•HCl for injection) are packaged in 8-cc (b)(4) amber glass tubing vials (w/ no overage). The vials are stoppered with 20-mm lyophilization stoppers, (b)(4) n.
- The description of the CCS for the 25-mg vials is provided in Table 1 (Section 3.2.P.7):

Table 1: Description of Packaging Components

Packaging Component	Description	Manufacturer
Vial	(b)(4) Amber Glass Tubing	(b)(4)
Stopper	20-mm (b)(4) Lyophilization Stopper	
Aluminum Flip-off Seal	20-mm Aluminum Flip-off Seal	

NA = Not Applicable

Notes:

- The lyophilization stopper is identical to that currently used for the 100-mg vials. The aluminum flip-off seal does not contact the solution, and does not provide a barrier to microbial ingress, and is also identical to that currently used for the 100-mg vial with the exception of color. There CCS components will NOT be evaluated in this review beyond the overall assessment of stability and by this reference to the approved NDA 22-249 CCS (for the 100-mg vials).
- The new CCS component is the smaller (8-mL) (b)(4) amber glass tubing vial. According to Table 2, this vial is provided (b)(4) described in DMF (b)(4) The applicant provided the specifications for the 8-cc glass vials in Table 3 (reproduced below):

Table 3: Specifications for 8 cc (b)(4) Amber Glass Vial

Test Procedure	Acceptance Criteria
(b)(4)	

Notes: The specifications for the 8-cc glass vials are essentially identical to those, which were used for the 20-cc glass vials (used to package the currently approved 100-mg "for injection" product). The glass vials are tested against a quality standard. The only difference between the specifications for the two vials involves reference to (b)(4) . Both vials are fabricated from the same compendial type of glass, and meet the same requirements for (b)(4). The technical drawings of the vial, stopper, and crimp are NOT reproduced for this review.

Evaluation: *Adequate*. The composition and control of the CCS components are adequate for this supplement either by reference to approved NDA 22-249 (unchanged components), or by comparison of specifications for the new-sized component (8-cc glass vial). The ultimate evaluation of the CCS involves assessment of exhibit stability data.

- 3.2.P.8: STABILITY: The stability section was divided into three parts, summary and conclusion, data, and

The applicant is in the process of conducting stability studies on FOUR batches of bendamustine for injection, 25 mg/vial (three (b)(4) and one (b)(4) batch). (b)(4) ". The (b)(4) stability batches were packaged in 8-cc amber glass tubing vials, sealed with the same lyophilization stopper as the approved 100-mg vials, crimped with an aluminum seal, and packaged into light-protecting secondary packaging (paperboard carton).

The (b)(4) .

The applicant notes that all tests and analytical methods used in stability are the same as those currently approved for NDA 22-249 (100-mg vials). The stability studies are being conducted under ICH conditions of refrigerated conditions (5ºC/ambient humidity), long-term storage (25ºC/60% RH), and accelerated conditions (40ºC/75% RH). All stability samples were store din the inverted position, in order to maximize contact with the stopper.

The stability protocol for refrigerated and long-term (room-temperature) conditions involves testing at 3, 6, 9, 12, 18, 24, and 36 months. Accelerated stability involves testing at 0, 1, 3, and 6 months.

Data is available (b)(4)

The applicant provided a statistical analysis of the assay and total impurities for the supportive batch of 25-mg vial along with three batches of the approved 100-mg vials.

On the basis of stability data for the (b)(4) and comparative stability for the approved 100-mg vials, the applicant is proposing that the existing expiration dating period and storage conditions for the 100-mg vials (24 months with storage at 25ºC with excursions permitted to 30ºC be applied to the 25-mg vials.

The applicant summarized the exhibit stability data results as follows:

- Assay (Table 6): th (b)(4) .
  The lower limit for assay is 90.0%. (b)(4)
- Impurities (Table 7): (b)(4)
- Reconstitution time (Table 8): Reconstitution time was essentially unchanged throughout the stability studies (no trends observed).
- pH (Table 9) was also essentially unchanged throughout the stability studies (all results were either (b)(4)).
- (b)(4)

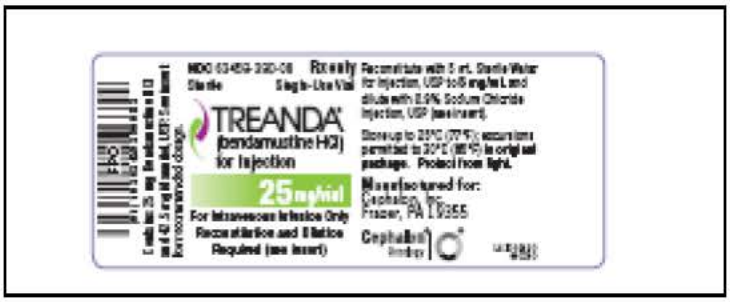
The summary results were verified by examining the compiled stability data (section 3.2.P.8.2).

Statistical evaluation: The applicant provided graphs with trend lines for assay and impurities for the supportive batch (25-mg vials) and historical batches of 100-mg vials. The slopes of the assay and impurity determination lines were essentially identical.

Evaluation: *Adequate*. The proposed expiration period (24 months with storage at 25ºC and excursions allowed to 30ºC) is acceptable for the 25-mg vials.

LABELING:
The applicant provided representative container and carton labels along with a revised package insert.

Container label:

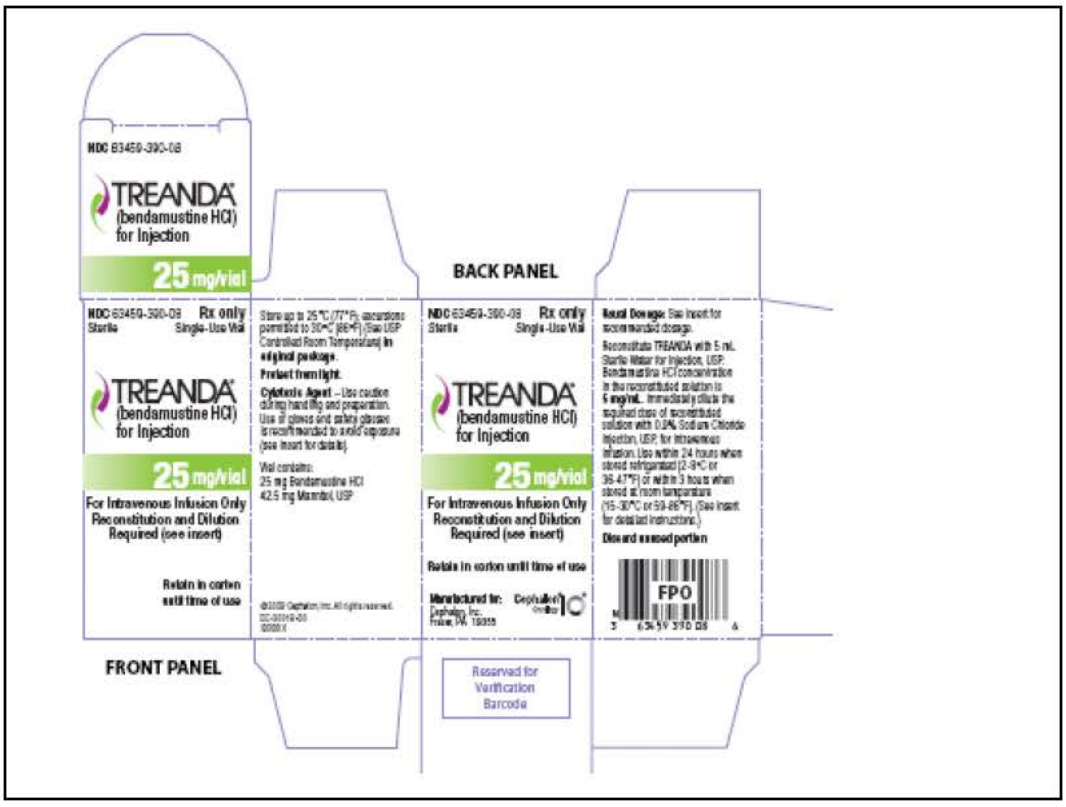


The container label indicates the new strength, provides the formulation, gives the storage conditions, and includes the NDC number 63459-390-08. (b)(4)

(b)(4)

Evaluation: *Adequate.*

Carton Label:



Evaluation: *Adequate.* The same text revisions apply to the carton label as the container label.

PACKAGE INSERT:
The changes in the package insert involve the following sections:

- DOSAGE FORMS AND STRENGTHS: Indicate availability of a 25 mg vial as a lyophilized powder.
- DOSAGE AND ADMINISTRATION: Provided reconstitution instructions for the 25-mg vial. Indicates that this strength is to be reconstituted with 5 mL of sterile water for injection, USP. It is noted that the final concentration of the reconstituted solution is the same for either vial (100-mg or 25-mg), and the subsequent instructions for secondary dilution (in 500 mL of NS) are also unchanged.
- DESCRIPTION SECTION: Added description of the 25 mg vial (contains 25 mg of bendamustine hydrochloride and 42.5 mg of mannitol).
- HOW SUPPLIED: Lists NDC 63549-390-08, TREANDA (bendamustine hydrochloride) for Injection, 25 mg in 8 mL amber single-use vial. It is noted that the NDC number for the 100-mg vial is 63549-391-20.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Lewis
12/23/2008 10:49:13 AM
CHEMIST
Recommend APPROVAL from the standpoint of CMC.

Hasmukh Patel
12/23/2008 10:53:09 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249/S-1

PRODUCT MICROBIOLOGY REVIEW

Product Quality Microbiology Review

22-DECEMBER-2008

NDA: 22-249/SCS-001

Drug Product Name
Proprietary: TREANDA®
Non-proprietary: bendamustine® HCl
Drug Product Priority Classification: Standard

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
8/27/08	8/28/08	9/24/08	9/29/08

Submission History (for amendments only): Not applicable

Applicant/Sponsor
Name: Cephalon, Inc.
Address: 41 Moores Road
Frazer, PA

Representative: Shirley Speer
Telephone: (610) 883-5765

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior approval supplement

2. SUBMISSION PROVIDES FOR: New 25 mg/vial presentation

3. MANUFACTURING SITE: Pharmachemie B.V.
Swensweg 5
2003 RN Haarlem
The Netherlands

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Lyophilized solid for injection
- Intravenous infusion
- 25 mg/vial

5. METHOD(S) OF STERILIZATION: (b)(4)

6. PHARMACOLOGICAL CATEGORY: Cancer therapy

B. SUPPORTING/RELATED DOCUMENTS: Product quality microbiology reviews of NDA 22-249 and 22-249-BC were completed on December 17, 2007 and February 6, 2008 respectively.

C. REMARKS: The application was provided in eCTD format. The 100 mg/vial presentation of TREANDA (NDA 22-249) was approved on March 20, 2008.

filename: N022249S001R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 22-249/SCS-001 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The applicant seeks approval for a 25 mg/vial presentation of the drug product. The 25 mg/vial presentation will be manufactured at the same facility using the (b)(4) . However, the 25 mg/vial presentation will (b)(4)

B. Brief Description of Microbiology Deficiencies -

No deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies -

Not applicable.

III. Administrative

A. Reviewer's Signature

Stephen E. Langille, Ph.D.

B. Endorsement Block

James McVey – Team Leader

C. CC Block

N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

Not applicable

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product –
  Bendamustine HCl for Injection is a sterile, non-pyrogenic lyophilized product for intravenous administration. The 100 mg/vial presentation has been approved by the FDA. The applicant seeks approval for an alternate 25 mg/vial presentation and an alternate container closure system.

- Drug product composition –
  The applicant does not propose any changes to the approved drug product formulation.

- Description of container closure system –
  A description of the container closure system to be used for the 25 mg/vial presentation is provided in Table 1 below:

Table 1: Container Closure System for the 25 mg/vial Presentation

Packaging Component	Description	Manufacturer
Vial	(b)(4) Amber Glass Tubing	(b)(4)
Stopper	20-mm (b)(4) Lyophilization Stopper	
Aluminum Flip-off Seal	20-mm Aluminum flip-off Seal	

The 100 mg/vial presentation is packaged in (b)(4) Amber Glass Tubing vials and the same stopper/seal combination proposed for the 25 mg/vial presentation.

Satisfactory

P.2 Pharmaceutical Development

Not applicable

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity –
  Because the proposed 25 mg/vial presentation will use the same stopper and a vial with the same neck diameter, additional container closure integrity studies were not required. However, the results of container closure integrity testing conducted on long term stability batches were provided in Table 1 of section P.2.5. All lots tested passed (b)(4) container closure integrity test at each time point.

- Preservative Effectiveness –
  Not applicable

- Justification for not having a microbial limit specification for a non-sterile drug product -
  Not applicable

Satisfactory

P.3 Manufacture

P.3.1 Manufacturers

The drug product will be manufactured in the same facility approved for the 100 mg/vial presentation:

Pharmachemie B.V.
Swensweg 5
2003 RN Haarlem
The Netherlands

P.3.3 Description of the Manufacturing Process and Process Controls

All major pieces of equipment used to manufacture the 25 mg/vial presentation are the same as those used to manufacture the approved 100 mg/vial presentation. A list of the key processing equipment and its location within the manufacturing facility is provided in Table 2 below:

Table 2: Key Processing Equipment for the 25 mg/vial Presentation

Equipment	Location	Room Classification
(b)(4)		

Satisfactory

P.3.5 Process Validation and/or Evaluation

(b)(4)

- (b)(4)

- (b)(4)

- (b)(4) (b)(4)
- (b)(4)
- (b)(4) .

Satisfactory

P.5 Control of Drug Product

P.5.1 Specifications

Sterility testing of the drug product will be conducted according to USP (b)(4)

P.5.2 Analytical Procedures

- Endotoxin –
  Endotoxin testing will be conducted according (b)(4)

- Sterility –
  Sterility testing will be conducted according (b)(4)

P.7 Container Closure System

See section P.1 of this review.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Long term stability testing is currently being conducted on four batches of the 25 mg/vial presentation.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

- Container Closure integrity –
  Sterility testing will be conducted (b)(4) .

- Endotoxin –
  Endotoxin testing will be conducted on [redacted] (b)(4)

P.8.3 Stability Data
The applicant states on p. 6 of section P.8.1 that the four stability lots tested are within specification criteria for sterility and endotoxin.

Satisfactory

A APPENDICES
Not applicable

R REGIONAL INFORMATION
Not applicable

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT
The package insert states that the lyophilized 25 mg/vial drug product should be reconstituted with 5 mL of sterile saline. Within 30 minutes of reconstitution, the solution should be withdrawn from the vial and aseptically transferred to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP. Once diluted in the 0.9% Sodium Chloride Injection, USP, the final admixture may be stored for 24 hours at 2-8°C or for 3 hours at room temperature 15-30°C.

Satisfactory

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:
Not applicable

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/s/

Stephen Langille
12/23/2008 09:20:46 AM
MICROBIOLOGIST

James McVey
12/23/2008 09:30:41 AM
MICROBIOLOGIST
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249/S-1

OTHER REVIEW

Division of Drug Oncology Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 22-249/S-001

Name of Drug: TREANDA® (bendamustine hydrochloride) for Injection, for intravenous infusion

Sponsor: Cephalon

Material Reviewed

Submission Date: August 27, 2008

Receipt Date: August 28, 2008

Background and Summary Description: NDA 22-249 is approved and indicated for the treatment of patients with Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin's Lymphoma (NHL). SCS-001 provides for the addition of a 25 mg vial. Currently, a 100 mg vial is approved under NDA 22-249. This supplement was also reviewed by the Chemistry and Microbiology Reviewers. See reviews each dated December 23, 2008.

Review

The submitted draft package, identified as "Label Code: PI-40014-XX" was compared to the package insert, identified as "Label Code: PI-40014-01", which was approved on October 31, 2008. The approved label is updated and identified as "Revised: 04/2009"

The following revisions were noted. For ease of review, the entire Package Insert is provided here.

Conclusions

Review Comments # 1, 3, 8 are acceptable revisions.
Review Comments # 2, 4, 5, 6, 7: The December 23, 2008 Chemistry and Microbiology reviews found these revisions acceptable.

The supplement should be APPROVED.

_____
Milinda Vialpando
Regulatory Project Manager

_____
Alice Kacuba, RN, MSN, RAC
Chief Project Management Staff

Nine (9) pages have been withheld as (b)(4), as draft labeling, immediately following this page.

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/s/

Milinda Vialpando
4/24/2009 01:57:56 PM
CSO

Alice Kacuba
4/24/2009 02:18:38 PM
CSO

Division of Drug Oncology Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 22-249/S-001

Name of Drug: TREANDA (bendamustine HCl) for injection

Sponsor: Cephalon

Material Reviewed

Submission Date: August 27, 2008

Receipt Date: August 28, 2008

Background and Summary Description: NDA 22-249 is approved and indicated for the treatment of patients with Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin's Lymphoma (NHL). SCS-001 provides for the addition of a 25 mg vial. Currently, a 100 mg vial is approved under NDA 22-249. This supplement was also reviewed by the Chemistry and Microbiology Reviewers. See reviews each dated December 23, 2008.

Review

The submitted draft package, identified as "Label Code: PI-40014-XX" was compared to the package insert, identified as "Label Code: PI-40014-01", which was approved on October 31, 2008.

Deletions are shown as ~~strikeouts~~ and additions are shown as <u>double underlines</u>. The following revisions were noted. For ease of review, the entire Package Insert is provided here.

Package insert

Conclusions

Review Comments # 1, 3, 8 are acceptable revisions.
Review Comments # 2, 4, 5, 6, 7: The December 23, 2008 Chemistry and Microbiology reviews found these revisions acceptable.

The supplement should be APPROVED.

_____	_____
Milinda Vialpando	Alice Kacuba, R.N., M.S.N., R.A.C.
Regulatory Project Manager	Chief Project Management Staff

Nine (9) pages have been withheld as (b)(4), as draft labeling, immediately following this page.

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/s/

Milinda Vialpando
4/17/2009 02:24:09 PM
CSO