CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:

NDA 22249/S-015

Trade Name: TREANDA Injection, for intravenous infusion, 90 mg/mL, available in 45 mg/0.5 mL single-use vial and 180 mg/2 mL single-use vial

Generic Name: bendamustine hydrochloride

Sponsor: Cephalon, Inc. (a wholly owned subsidiary of Teva Pharmaceuticals, Ltd.)

Approval Date: September 13, 2013

This supplemental new drug application provides for a new liquid formulation of TREANDA that is intended to replace the existing lyophilized powder formulation of TREANDA.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Division Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22249/S-015

APPROVAL LETTER

Cephalon, Inc. (a wholly owned subsidiary of Teva Pharmaceuticals, Ltd.)
Attention: Michael J. McGraw, PharmD, MS
Director, Regulatory Affairs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Dear Dr. McGraw:

Please refer to your Supplemental New Drug Application (sNDA) dated March 8, 2013, received March 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TREANDA (bendamustine hydrochloride) lyophilized solid for injection, 25 mg/vial; 100mg/vial.

We acknowledge receipt of your amendments dated April 26, May 6, May 10, May 21, May 30, June 3, June 7, June 12, June 21, June 27, June 28, August 29, and September 5, 2013.

The July 26, 2013, submission constituted a complete response to our July 2, 2013, action letter.

This supplemental new drug application provides for a new liquid formulation of TREANDA that is intended to replace the existing lyophilized powder formulation of TREANDA.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

Based on provided stability data, a 12-month expiration dating period is granted for the drug product when stored at 2° to 8°C (36° to 46°F) in the original package in cartons.

At the next printing correct the following sentence found in Section 2.3 Preparation for Intravenous Administration:

> Current: "Aseptically withdraw the volume needed for the required dose from the 90 mg/mL solution TREANDA Injection vial."
>
> Recommended: Aseptically withdraw the volume needed for the required dose from the 90 mg/mL solution.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on June 28, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22249/S-015**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Hasmukh Patel, Ph.D.
Branch Chief, Branch III
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

HASMUKH B PATEL
09/13/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

OTHER ACTION LETTER(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022249/S-015 (b) (4)

COMPLETE RESPONSE

Cephalon, Inc. (a wholly owned subsidiary of Teva Pharmaceuticals, Ltd.)
Attention: Michael J. McGraw, PharmD, MS
Director, Regulatory Affairs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Dear Dr. McGraw:

Please refer to your Supplemental New Drug Applications (sNDA) S-015 dated March 8, 2013, received March 8, 2013, (b) (4) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TREANDA (bendamustine hydrochloride) lyophilized solid for injection, 25 mg/vial; 100mg/vial.

We acknowledge receipt of your amendments dated March 22, April 26, May 6, May 10 (2), May 21, May 30, June 3, June 7, June 12, June 21, June 27 (3), and June 28, 2013.

This "Prior Approval" Chemistry, Manufacturing, and Controls supplemental new drug application (S-015) proposes a new liquid formulation of TREANDA that is intended to replace the existing lyophilized powder formulation of TREANDA.

(b) (4)

We have completed the review of your applications, as amended, and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. (b) (4)

(b) (4) as recommended in our June 17th, 2013 information request letter.

LABELING

2. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

3. As stated (b) (4) is unacceptable. In responding to the deficiencies associated with S-015, please include your request for (b) (4) review and submit the request for (b) (4) review to S-015.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Theresa Carioti, Regulatory Project Manager, at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
07/02/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

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) Injection, for intravenous infusion
Initial U.S. Approval: 2008

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

Dosage and Administration,	
Preparation for Intravenous Administration (2.3)	XX/2013
Dosage and Administration, Admixture Stability (2.4)	XX/2013

----------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----------

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 must be diluted prior to infusion. (2.3)

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

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

----------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. (2.1) Complications of myelosuppression may lead to death. (5.1)
- Infections: Monitor for fever and other signs of infection 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: 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 ≥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 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 0X/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- **1.1** Chronic Lymphocytic Leukemia (CLL)
- **1.2** Non-Hodgkin Lymphoma (NHL)

2 DOSAGE AND ADMINISTRATION
- **2.1** Dosing Instructions for CLL
- **2.2** Dosing Instructions for NHL
- **2.3** Reconstitution/Preparation for Intravenous Administration
- **2.4** Admixture Stability

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- **5.1** Myelosuppression
- **5.2** Infections
- **5.3** Anaphylaxis and Infusion Reactions
- **5.4** Tumor Lysis Syndrome
- **5.5** Skin Reactions
- **5.6** Other Malignancies
- **5.7** Extravasation
- **5.8** Embryo-fetal Toxicity

6 ADVERSE REACTIONS
- **6.1** Clinical Trials Experience in CLL
- **6.2** Clinical Trials Experience in NHL
- **6.3** Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- **8.1** Pregnancy
- **8.3** Nursing Mothers
- **8.4** Pediatric Use
- **8.5** Geriatric Use
- **8.6** Renal Impairment
- **8.7** Hepatic Impairment
- **8.8** Effect of Gender

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- **12.1** Mechanism of Action

12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Chronic Lymphocytic Leukemia (CLL)
14.2 Non-Hodgkin Lymphoma (NHL)
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 Safe Handling and Disposal
16.2 How Supplied
16.3 Storage
17 PATIENT COUNSELING INFORMATION

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

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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 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 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 Preparation for Intravenous Administration

Each vial of TREANDA Injection is intended for single use only. Aseptically withdraw the volume needed for the required dose from the 90 mg/mL solution TREANDA Injection vial.

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. 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.

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.

2.4 Admixture Stability

TREANDA Injection 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 under refrigerated conditions at 2°-8°C (36°-46°F) or for 2 hours when stored at room temperature 15°-30°C (59°-86°F) and room light. Administration of TREANDA must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

TREANDA Injection is supplied in single-use vials containing either 45 mg/0.5 mL or 180 mg/2 mL of bendamustine HCl.

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 (2.1) and (2.2)]*

5.2 Infections

Infection, including pneumonia, sepsis, septic shock, and death have 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.

5.3 Anaphylaxis and Infusion Reactions

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

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome associated with TREANDA treatment has occurred in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. 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/m^2) 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)]*

The data described below reflect exposure to TREANDA in 329 patients who participated in an actively-controlled trial (N=153) for the treatment of CLL and two single-arm trials (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.

6.1 Clinical Trials Experience in CLL

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/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. 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 ≥ 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 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.

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 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)
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 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.

6.3 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: anaphylaxis; and injection or infusion site reactions including phlebitis, pruritus, irritation, pain, and swelling; pneumocystis jiroveci pneumonia and pneumonitis.
Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. *[See Warnings and Precautions (5.5)]*

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 (5.8)]*

Risk Summary
TREANDA can cause fetal harm when administered to a pregnant woman. Bendamustine caused malformations in animals, when a single dose was administered to pregnant animals. Advise women to avoid becoming pregnant while receiving TREANDA and for 3 months after therapy has

stopped. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to a fetus. Advise men receiving TREANDA to use reliable contraception for the same time period.

Animal data
Single intraperitoneal doses of bendamustine from 210 mg/m2(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/m2 (25 mg/kg) and an increase in abnormalities from 112.5 mg/m2 (37.5 mg/kg) similar to those seen after a single intraperitoneal administration. Single intraperitoneal doses of bendamustine from 120 mg/m2 (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 effectiveness of TREANDA in pediatric patients has not been established. TREANDA was evaluated in a single Phase 1/2 trial in pediatric patients with leukemia. The safety profile for TREANDA in pediatric patients was consistent with that seen in adults, and no new safety signals were identified.
The trial included pediatric patients from 1-19 years of age with relapsed or refractory acute leukemia, including 27 patients with acute lymphocytic leukemia (ALL) and 16 patients with acute myeloid leukemia (AML). TREANDA was administered as an intravenous infusion over 60 minutes on Days 1 and 2 of each 21-day cycle. Doses of 90 and 120 mg/m^2 were evaluated. The Phase 1 portion of the study determined that the recommended Phase 2 dose of TREANDA in pediatric patients was 120 mg/m^2.
A total of 32 patients entered the Phase 2 portion of the study at the recommended dose and were evaluated for response. There was no treatment response (CR+ CRp) in any patient at this dose. However, there were 2 patients with ALL who achieved a CR at a dose of 90 mg/m^2 in the Phase 1 portion of the study.
In the above-mentioned pediatric trial, the pharmacokinetics of TREANDA at 90 and 120 mg/m^2 doses were evaluated in 5 and 38 patients, respectively, aged 1 to 19 years (median age of 10 years).
The geometric mean body surface adjusted clearance of bendamustine was 14.2 L/h/m^2. The exposures (AUC_{0-24} and C_{max}) to bendamustine in pediatric patients following a 120 mg/m^2 intravenous infusion over 60 minutes were similar to those in adult patients following the same 120 mg/m^2 dose.

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 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 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

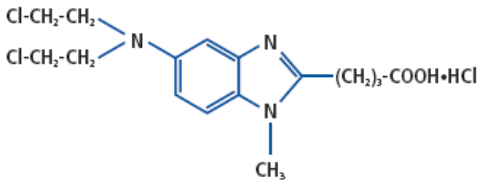
The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

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

Bendamustine hydrochloride is an alkylating agent . 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) Injection is intended for intravenous infusion only after 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 clear colorless to yellow solution in single-use vials at the concentration of 90 mg/mL of bendamustine HCl. Each 0.5 mL vial contains 45 mg of bendamustine hydrochloride, 162 mg of Propylene Glycol, USP and 293 mg of N,N-Dimethylacetamide, EP. Each 2 mL vial contains 180 mg of bendamustine hydrochloride, 648 mg of Propylene Glycol, USP and 1172 mg of N,N-Dimethylacetamide, EP. An overfill of 0.2 mL is included in each vial.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

The effect of bendamustine on the QTc interval was evaluated in 53 patients with indolent NHL and mantle cell lymphoma on Day 1 of Cycle 1 after administration of rituximab at 375 mg/m^2 intravenous infusion followed by a 30-minute intravenous infusion of bendamustine at 90 mg/m^2/day. No mean changes greater than 20 milliseconds were detected up to one hour post-infusion. The potential for delayed effects on the QT interval after one hour was not evaluated.

12.3 Pharmacokinetics

Absorption

Following a single IV dose of bendamustine hydrochloride 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 a mass balance study, plasma radioactivity levels were sustained for a greater period of time than plasma concentrations of bendamustine, γ hydroxybendamustine (M3), and N desmethylbendamustine (M4). This suggests that there are bendamustine derived materials (detected via the radiolabel), that are rapidly cleared and have a longer half-life than bendamustine and its active metabolites.

The mean steady-state volume of distribution (V_{ss}) of bendamustine was approximately 20-25 L. Steady-state volume of distribution for total radioactivity was approximately 50 L, indicating that neither bendamustine nor total radioactivity are extensively distributed into the tissues.

Metabolism

In vitro data indicate that bendamustine is primarily metabolized via hydrolysis to monohydroxy (HP1) and dihydroxy-bendamustine (HP2) metabolites with low cytotoxic activity. Two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are $1/10^{th}$ and $1/100^{th}$ that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to bendamustine.

Results of a human mass balance study confirm that bendamustine is extensively metabolized via hydrolytic, oxidative, and conjugative pathways. *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

Mean recovery of total radioactivity in cancer patients following IV infusion of [^{14}C] bendamustine hydrochloride was approximately 76% of the dose. Approximately 50% the dose was recovered in the urine and approximately a 25% of the dose was recovered in the feces. Urinary excretion was confirmed as a relatively minor pathway of elimination of bendamustine, with approximately 3.3% of the dose recovered in the urine as parent. Less than 1% of the dose was recovered in the urine as M3 and M4, and less than 5% of the dose was recovered in the urine as HP2.

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 adult 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.

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 65.7x109/L vs. 65.1x109/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).
Patients were randomly assigned to receive either TREANDA at 100 mg/m2, administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL1.
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 ration (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.

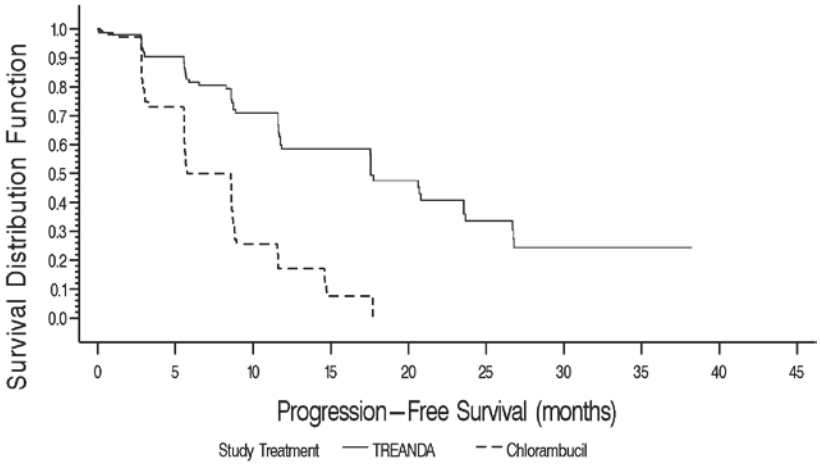
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

† 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 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). 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. OSHA Hazardous Drugs. OSHA. [Accessed on June 19, 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index html]

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 Injection. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If 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.
TREANDA is a cytotoxic drug. Follow special handling and disposal procedures[1]

16.2 How Supplied

TREANDA (bendamustine hydrochloride) Injection is supplied as a 90 mg/mL clear colorless to yellow solution as follows:

NDC 63459-395-02: 45 mg/0.5 mL of solution in an amber single-use vial
NDC 63459-396-02: 180 mg/2 mL of solution in an amber single-use vial

Vials are supplied in individual cartons.

16.3 Storage

TREANDA Injection must be stored refrigerated between 2°-8°C (36°-46°F). Retain in original package until time of use to protect from light.

17 PATIENT COUNSELING INFORMATION

Allergic (Hypersensitivity) Reactions
Inform patients of the possibility of mild or serious allergic reactions and to immediately report rash, facial swelling, or difficulty breathing during or soon after infusion.

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

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.

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.

TRE-XXX

Distributed By:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

CHEMISTRY REVIEW(S)

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch III)
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 22249/S-015**

2. **Assigned Date:** 22-Mar-2013
   PDUFA Goal Date: 08-Jul-2013
   Review Date: 02-Jul-2013

3. **Review #: 1**

4. **Submissions Being Reviewed**

Supplement Number	DARRTS SD Number	Submission Date	CDER Stamp Date
S-015 PAS supplement	316	08-Mar-2013	08-Mar-2013
Amendment (draft container and carton labeling)	318	22-Mar-2013	22-Mar-2013
Amendment (response to FDA request for contact information for facilities)	325	26-Apr-2013	26-Apr-2013
Amendment (response to FDA questions 1-3 of issues discussed in the 5/3/13 teleconference)	326	06-May-2013	07-May-2013
Amendment (response to FDA questions 4-8 of issues discussed in the 5/3/13 teleconference)	329	10-May-2013	10-May-2013
Amendment (response to FDA 5/22/13 request to update Module 3)	337	30-May-2013	31-May-2013
Amendment (response to FDA 6/5/13 IR)	343	12-Jun-2013	13-Jun-2013
Amendment (response to FDA 6/17/13 IR)	344	21-Jun-2013	21-Jun-2013
Amendment (response to 6/26/13 CMC and DMEA comments)	345	27-Jun-2013	27-Jun-2013
Amendment (revised container labels and carton labeling in response to 6/26/13 CMC and DMEA comments)	347	27-Jun-2013	27-Jun-2013
Amendment (response to FDA PK reviewer's IR)	348	28-Jun-2013	28-Jun-2013

5. **Proposed Changes:** This Prior Approval Supplement proposes a new liquid formulation to replace the existing lyophilized formulation of Treanda. There is no change in the bendamustine hydrochloride drug substance.

6. **Clinical Review Division:** Division of Hematology Products

7. **Name and Address of Applicant:**

   Cephalon, Inc. (a wholly owned subsidiary of Teva Pharmaceuticals, Ltd.)
   Attention: Sherri Carenzo, Manager, Regulatory Affairs
   41 Moores Road, P.O. Box 4011
   Frazer, PA 19355

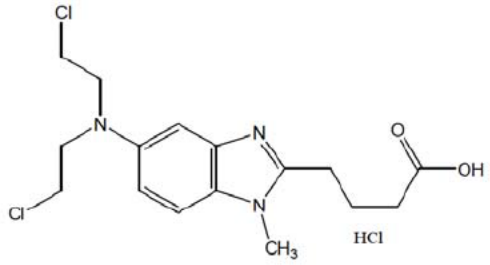
   Email address: Sherri.Carenzo@tevapharm.com

8. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC
Treanda® (bendamustine hydrochloride) Injection	Injection	45 mg/0.5 mL 180 mg/2 mL	Intravenous infusion	Rx

*Reviewer's note: The currently approved dosage form in NDA 22249 is lyophilized powder for injection.

9. Chemical name and structure of drug substance:



USAN: Bendamustine Hydrochloride

Chemical name:
1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride.

CAS Number: 3543-75-7; 16506-27-7 (bendamustine).
Molecular formula: $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$
MW: 394.72

10. Supporting/Relating Document:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		4	N/A	See current review	See section 3.2.P.7
	III			3	Adequate	22-Jul-2009	Reviewed by Zedong Dong*
				3	Adequate	03-Sep-2009	Reviewed by Ravindra Kasliwal**
	V			3	Adequate	02-Mar-2012 & 26-Apr-2013	Reviewed by Marla Stevens Riley***.

Reviewer's note:
*This is the CMC Review of the 5/8/2009 amendment of DMF (b) (4) for (b) (4). This 5/8/2009 amendment is the current DMF location that is provided in (b) (4) Letter of Authorization (LOA) for (b) (4) (b) (4) (see section 1.4 of the supplement for the LOA).
** This is the CMC Review of the 12/28/2006 amendment of DMF (b) (4) for (b) (4) This 12/28/2006 amendment is the current DMF location that is provided in (b) (4) Letter of Authorization for (b) (4) (b) (4). See section 1.4 of the supplement for the LOA.
*** This is the Microbiology Review of the 11/22/11 annual update for (b) (4), which is the current DMF location that is provided in (b) (4) LOA for DMF (b) (4) for (b) (4) Note a more recent review of the (b) (4) provided in the 1/24/13 annual update has been reviewed by Scott Steffen in his review dated 4/26/13. Please also see the 06-Jun-2013 microbiology review of this NDA supplement.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

11. Consults/CMC Related Reviews:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	25-Jun-2013	Christina Capacci-Daniel
Pharm/Tox	See note below*	17-Jun-2013	Ramadevi Gudi
Biopharm	Approval	26-Jun-2013 & 02-Jul-2013	Houda Mahayni
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	The proposed (b) (4) is not acceptable.	13-Jun-2013 (for (b) (4)	Kevin Wright
Microbiology	Approval	06-Jun-2013	Erika Pfeiler
Clinical Pharmacology	See note below**	01-Jul-2013	Rachelle M Lubin

*The following issues were consulted to pharm/tox reviewers:

- Acceptance criteria of degradants in the drug product specification
- Acceptability of container closure leachables
- Acceptability of the levels of inactive ingredients N,N-dimethylacetamide and propylene glycol in the formulation

In addition to the pharm/tox review in DARRTS, please also see the "e-mail correspondences" section of this review (page 81) for pharm/tox reviewers' response to these issues.

**The clinical pharmacology reviewer was consulted to verify whether the applicant's claim that exposure to CEP-43714 (HP1) in humans during clinical studies was about 10% relative to bendamustine, based on clinical study reports cited in the 6/27/13 amendment. The clinical pharmacology reviewer concluded that the HP1 level was measured using an unvalidated bioanalytical method and therefore deferred to CMC regarding acceptability of the limits for (b) (4) degradant.

12. Summary/Remarks

This Prior Approval Supplement proposes a new liquid formulation to replace the existing lyophilized formulation of Treanda. Treanda is currently approved as a single-use vial containing 25 mg/vial or 100 mg/vial of bendamustine hydrochloride as a lyophilized powder that is reconstituted with Sterile Water for Injection, USP. The proposed new formulation will be a single-use vial containing either 45 mg/0.5 mL or 180 mg/2 mL of bendamustine hydrochloride as a sterile solution formulation. The solution will be aseptically withdrawn and transferred into a 500 mL infusion bag of either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection to produce the same concentration as the

original formulation prior to intravenous infusion. There is no change in the bendamustine hydrochloride drug substance.

The powder for injection formulation was approved on 3/20/2008 under this NDA. It is noted that the approved formulation has included bendamustine hydrochloride, the salt form, in the nonproprietary name for the drug product, rather than the active moiety bendamustine. According to MAPP 5021.1 (Naming of Drug Products Containing Salt Drug Substances, Effective 2/20/13), CDER will apply the exception to the USP Salt Policy when the name of the salt is necessary to maintain consistency with other dosage forms of the same active ingredient (salt). Therefore, bendamustine hydrochloride, the salt form, will continue to be used in the nonproprietary name and as the basis of strength for this new dosage form.

The proposed solution formulation contains (b) (4) propylene glycol and (b) (4) N,N- dimethylacetamide. The levels (b) (4) in the formulation have been found acceptable by the nonclinical reviewers.

The risk of potential leachables is also a concern as (b) (4) (b) (4) Detailed extractable/leachable studies on the glass vial and rubber stoppers (with FluroTec coating) are provided. A batch of bendamustine HCl solution stored at 5°C (the proposed storage temperature) in the inverted position for 42 months was tested for the selected leachables. The levels of leachables were found acceptable by the nonclinical reviewers.

Two new degradants, (b) (4) and (b) (4) are found in the solution formulation. These two degradants are (b) (4) (b) (4). These degradants do not exist in the lyophilized powder formulation as the powder formulation (b) (4). The acceptance criteria for these two new degradants in the drug product specification have been found acceptable by the nonclinical reviewers.

The concentration of the solution (90 mg/mL) appears to be very different from that of the current reconstituted solution for Treanda (which is 5 mg/ mL). There is a concern for medication errors that may arise due to such a high concentration. The applicant addressed this issue in the 10-May-2013 amendment in response to the FDA 03-May-2013 IR letter. The measures to minimize potential for medication errors include the difference in visual appearance, the requirement to calculate volume per patient per dose, and the (b) (4) (b) (4) planned. The clinical and DMEPA reviewers found the applicant's proposal to mitigate the risk of medication errors acceptable.

Based on the submitted stability data, a (b) (4) month expiration dating period is granted for the drug product when stored at 2° to 8°C (36° to 46°F) in the original package. This determination is based on ICH Q1A (R2) and ICH Q1E, where it is stated that, for drug products intended for storage in a refrigerator, if significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition. Extrapolation is not

considered appropriate. Please see Section 3.2.P.8.3 for more detailed discussion regarding this issue.

The Office of Compliance has issued an overall "acceptable" recommendation dated 25-Jun-2013 for all facilities used for manufacturing and control of the new formulation of the drug product.

The only pending issue is the stability of admixture solutions as described below:

As stated in the June 17, 2013 FDA information request letter, the compatibility study results, as provided in Section 3.2.P.2.6, do not support (b) (4) .

- It does not appear that (b) (4)
- The data provided in the 21-Jun-2013 amendment, which only contains results from final time points, indicate that the (b) (4)
- Study DP-2010-014, which was provided in the June 27, 2013 amendment, failed to support the applicant's claim that exposure to CEP-43714 in humans during clinical studies was about 10% relative to bendamustine levels. This study has been reviewed by the Clinical Pharmacology reviewers and found that the level of CEP-43714 was measured using an unvalidated bioanalytical method.

This NDA supplement can not been approved with the currently proposed storage conditions on the labeling for the final admixture solutions.

13. Conclusions & Recommendations:

From the perspective of chemistry, manufacturing, and controls, this supplement can not be approved without satisfactory resolution of the in-use stability issues.

Include the following comments in the Complete Response letter:

(b) (4)

(b) (4)

as recommended in our June 17th, 2013 information request letter.

14. Primary Reviewer: Sue-Ching Lin, CMC reviewer, ONDQA

Secondary Reviewer: Hasmukh Patel, Ph.D., Branch Chief, Branch III, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

(See appended electronic signature page)

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b. (b) (4)

c.

IR #4: The following information was requested from the applicant on 26-Jun-2013:

The following comments pertain to the carton labeling:

1. *Revise the admixture stability information to read "Use the final solution* (b) (4) *hours when stored refrigerated at 2°-8°C (36°-46°F). See insert for details."*

2. *Delete "* (b) (4) *" from the storage statement.*

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

/s/

SUE CHING LIN
07/02/2013

NALLAPERUM CHIDAMBARAM
07/02/2013
for Dr. Hasmukh Patel

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch III)
Review of Chemistry, Manufacturing, and Controls

1. **NDA Number: 22249**

2. **Submission Being Reviewed**

Supplement Number	DARRTS SD Number	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
S-015 Resubmission	349	26-Jul-2013	26-Jul-2013	26-Jul-2013	26-Nov-2013	09-Sep-2013
Amendment	352	29-Aug-2013	29-Aug-2013	29-Aug-2013		
Amendment	355	05-Sep-2013	05-Sep-2013	05-Sep-2013		

3. **Proposed Changes:** This Prior Approval Supplement proposes a new liquid formulation to replace the existing lyophilized formulation of Treanda. There is no change in the bendamustine hydrochloride drug substance.

4. **Review #: 2**

5. **Clinical Review Division:** Division of Hematology Products

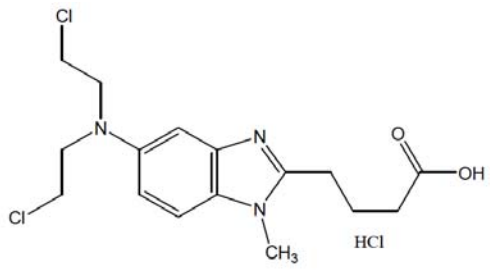
6. **Name and Address of Applicant:**
Cephalon, Inc. (a wholly owned subsidiary of Teva Pharmaceuticals, Ltd.)
Attention: Sherri Carenzo, Manager, Regulatory Affairs
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

7. **Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC
Treanda® (bendamustine hydrochloride) Injection	Injection	45 mg/0.5 mL 180 mg/2 mL	Intravenous infusion	Rx

*Reviewer's note: The currently approved dosage form in NDA 22249 is lyophilized powder for injection.

8. **Chemical name and structure of drug substance:**

	USAN: Bendamustine Hydrochloride Chemical name: 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride. CAS Number: 3543-75-7; 16506-27-7 (bendamustine). Molecular formula: $C_{16}H_{21}Cl_2N_3O_2 \bullet HCl$ MW: 394.72

9. Pharmacological Category/Indication: Treanda is an alkylating drug indicated for treatment of patients with chronic lymphocytic leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL).

10. Supporting/Relating Document:
CMC Review #1 dated 02-Jul-2013
FDA Complete Response letter dated 02-Jul-2013

11. Consults: Nonclinical consult regarding the acceptability of degradation products in admixtures

12. Summary/Remarks

This is a review of the 26-Jul-2013 resubmission and its subsequent amendments, which were submitted to address the deficiencies included in the FDA 02-Jul-2013 "Complete Response" letter.

In this resubmission, the applicant provided two admixture in-use stability reports, which were conducted in 2008 and 2009. Based on the data, the CMC review team, in consultation with the Nonclinical review team, recommends that storage of the admixture solutions for the proposed new solution formulation be restricted to a maximum of 2 hours when stored at room temperature (as opposed to the 3 hours of storage at room temperature for the currently marketed formulation). The applicant agrees with the Agency's recommendation and the labeling has been revised accordingly to limit the storage of admixture to a maximum of 2 hours at room temperature or for 24 hours under refrigerated condition.

The package insert, container labels, and carton labeling, as provided in this resubmission are acceptable from the CMC perspective. As indicated in the 8/15/13 e-mail from Yelena Maslov, DMEPA, the container labels and carton labeling are acceptable from the DMEPA perspective.

Stability updates were provided in the 8/29/13 amendment to provide 12-month primary stability data for the drug product stored at 5^{o}C in the upright and inverted positions. The applicant proposed a 12-month shelf-life for the drug product when stored under refrigerated conditions. Based on the submitted stability data, a 12-month expiration dating period is granted for the drug product when stored at 2° to 8°C (36° to 46°F) in the original package in cartons. This determination is based on the submitted accelerated and long-term primary stability data and in accordance with ICH Q1A (R2) and ICH Q1E.

13. Conclusions & Recommendations:

This supplement is recommended for approval from the CMC perspective. Please include the following language in the approval letter:

Based on the provided stability data, a 12-month expiration dating period is granted for the drug product when stored at 2° to 8°C (36° to 46°F) in the original package in cartons.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer: Sue-Ching Lin, CMC reviewer, ONDQA

Secondary Reviewer: Hasmukh Patel, Ph.D., Branch Chief, Branch III, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

(See appended electronic signature page)

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/s/

SUE CHING LIN
09/09/2013

NALLAPERUM CHIDAMBARAM
09/09/2013
I concur

for Dr. Hasmukh Patel

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 22249
Supporting document/s:	S-015
Applicant's letter date:	March 8, 2013
CDER stamp date:	March 8, 2013
Product:	Treanda (bendamustine hydrochloride)
Indication:	Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin Lymphoma (NHL).
Applicant:	Cephalon, Inc.
Review Division:	Division of Hematology and Oncology Toxicology (DHOT)
Reviewer:	Ramadevi Gudi, Ph.D.
Supervisor/Team Leader:	Haleh Saber, Ph.D.
Division Director:	John Leighton, DABT, Ph.D.
Project Manager:	Theresa A. Carioti, MPH

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 22249 are owned by Cephalon or are data for which Cephalon has obtained a written right of reference. Any information or data necessary for approval of 22249 that Cephalon does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 22249.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

1.1 INTRODUCTION 3
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 3
1.3 RECOMMENDATIONS 4

2 DRUG INFORMATION 4

2.1 DRUG 4
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS 5
2.3 DRUG FORMULATION 5
2.4 COMMENTS ON EXCIPIENTS 5
2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN 6
2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN 6
2.7 REGULATORY BACKGROUND 7

3 STUDIES SUBMITTED 7

3.1 STUDIES REVIEWED 7
3.2 STUDIES NOT REVIEWED 7
3.3 PREVIOUS REVIEWS REFERENCED 7

4 PHARMACOLOGY 7

5 PHARMACOKINETICS/ADME/TOXICOKINETICS 8

5.1 PK\PD 8

6 GENERAL TOXICOLOGY 10

6.2 REPEAT-DOSE TOXICITY 10

1 Executive Summary

1.1 Introduction

The current submission to NDA 22249 (Supporting Document 15) is a proposal to replace existing formulation of Treanda® (bendamustine HCl for injection) for the treatment of patients with Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin Lymphoma (NHL).

Treanda® is currently approved as a single-use vial containing 25 mg/vial or 100 mg/vial of bendamustine HCl as a lyophilized powder that is reconstituted with sterile water for injection, USP. The new proposed formulation will be a single-use vial containing 45 mg/vial or 180 mg/vial of bendamustine HCl as a sterile solution (b) (4) N,N dimethylacetamide (DMA) and (b) (4) propylene glycol (PG).

The amounts of PG and DMA in the proposed formulation are within the amounts present in FDA approved intravenous (I.V.) products.

1.2 Brief Discussion of Nonclinical Findings

A toxicology study was conducted in rats after repeated intravenous (IV) infusion of the to-be-marketed formulation of bendamustine. In this study bendamustine containing (b) (4) DMA and (b) (4) PG was spiked with two propylene glycol esters (PGE) of bendamustine. PGEs will be present in the drug product due to esterification of the drug substance with propylene glycol during manufacturing of the drug product and upon storage. The two PGEs expected to be present in the drug product and assessed in the toxicology study are referred to as (b) (4) and (b) (4) A ratio of 4:1, (b) (4), was used in the toxicology study. The control animals in this study received (b) (4) propylene glycol (PG) and (b) (4) dimethylacetamide (DMA). The animals were dosed once daily for 3 consecutive days followed by 18 days drug-free period (21-day cycle for 5 cycles) via a catheter implanted in a femoral vein.

Mortality occurred in control and treated animals throughout the study. Fourteen animals died or were sacrificed due to moribundity from all groups. Additional 13 animals from all groups with broken or retracted catheters were sacrificed prior to terminal sacrifice. Two mortalities, including one in the control group occurred shortly after blood collection. Swollen thorax, swollen inguinal region were observed in control and treated animals. The cause of death was considered as combination of chronic catheterization associated with inflammatory response. Hematological evaluations showed a dose related decrease in reticulocytes, platelets, white blood cells, lymphocytes, basophils and eosinophil counts in the bendamustine with or without PGE mixture. The main target organ of toxicity was kidney. Granular casts were observed in the urine sediment of males and females given high dose of bendamustine with or without PGE mixture. Renal tubular degeneration/necrosis and/or karyomegaly/cytomegaly were observed in males and females given bendamustine with

or without PGE mixture. Chronic progressive nephropathy and mononuclear cell infiltrates were observed in males and females given bendamustine with or without PGE or with the control article. Other toxicities were in the brain, heart, liver, and lung (mononuclear cell infiltration), heart (degenerative cardiomyopathy), kidney, bone marrow, femur and liver (hyperplasia). Systemic exposure to bendamustine and 2 circulating metabolites (M3 and M4) were generally dose-related and comparable with or without PGE over the range evaluated on all sampling days. The metabolites were present at much lower concentrations than the parent, bendamustine. The $t_{1/2}$ values ranged from 0.5 to 1 hr. Pharmacokinetic profiles of bendamustine and its two metabolites (M3 and M4) were similar to that reported with the currently marketed Treanda®. There are no new toxicities observed in the animals dosed with control article ((b) (4) PG and (b) (4) DMA) compared to animals dosed with bendamustine (to-be-marketed formulation) with added PGEs or bendamustine (to-be-marketed formulation) alone. Overall, there were no remarkable differences in toxicities observed in the bendamustine (to-be-marketed formulation) with added PGEs or bendamustine (to-be-marketed formulation) alone.

1.3 Recommendations

1.3.1 Approvability

Recommending approval.

1.3.2 Additional Non Clinical Recommendations

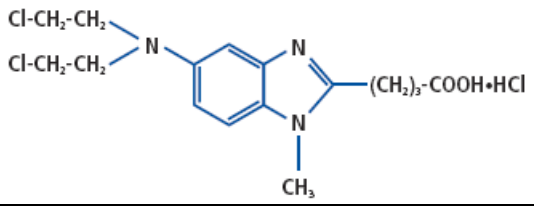
None.

1.3.3 Labeling

The change in the formulation will not affect the nonclinical sections of the label.

2 Drug Information

2.1 Drug

CAS Registry Number	Not provided
Generic Name	Bendamustine HCl
Code Name	CEP-18083
Chemical Name	1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride
Molecular Formula/ Molecular Weight	C16H21Cl2N3O2 · HCl and 394.7
Structure or Biochemical Description	
Pharmacologic of the drug	Alkylating drug

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 22249, NDA 22303

2.3 Drug Formulation

Commercial Formulation – Bendamustine Solution (Excerpted from Applicant's NDA)

Ingredient	Composition (% w/w)
Bendamustine HCl	90 mg
N,N-dimethylacetamide	586 mg
Propylene glycol	324 mg

2.4 Comments on Excipients

The proposed formulation contains (b) (4) N,N dimethylacetamide (DMA) and (b) (4) propylene glycol (PG).

The composition of the 90 mg/mL bendamustine solution, presented as 45 mg/0.5 mL and 180 mg/m/2.0 mL, and the function of each ingredient are listed below (excerpted from Applicant's NDA)

Table 1: Composition of the 45 mg/0.5 mL and 180 mg/2.0 mL Drug Products

Component	Reference to standard	Function	45 mg/0.5 mL		180 mg/2.0 mL	
			Amount per vial (weight)	Unit Formula	Amount per vial (weight)	Unit Formula
Bendamustine HCl	In house standard	Active ingredient	45 mg	45 mg	180 mg	180 mg
Propylene Glycol[3]	USP	(b) (4)	162 mg	0.16 mL	648 mg	0.62 mL
N,N-dimethylacetamide[4]	EP		293 mg	0.31 mL	1172 mg	1.24 mL
Total			0.5 mL[1]		2.0 mL[2]	

[1] Calculated volume; total weight is 500 mg with a density of 0.996 g/mL (corresponds to final mixed solution)
[2] Calculated volume; total weight is 2000 mg with a density of 0.996 g/mL (corresponds to final mixed solution)
[3] (b) (4)
[4]

According to the proposed label for the new formulation, bendamustine HCl will be administered intravenously at a recommended dose 100 mg/m^2 or 120 mgm^2 over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. Each 45-mg vial contains 45 mg of bendamustine hydrochloride, 162 mg of PG, and 293 mg of DMA. Each 180-mg vial contains 180 mg of bendamustine hydrochloride, 648 mg of PG and 1172 mg of DMA. In the approved formulation, Treanda® (bendamustine hydrochloride) does not contain N,N-dimethylacetamide (DMA) and propylene glycol (PG).

PG: There are several FDA approved I.V. products with high levels of PG, e.g. lorazepam contains 0.8 mL/mL or **80%** v/v of PG and diazepam contains 0.4 mL/mL or **40%** of PG.

DMA: The concentration of DMA for the highest proposed dose (120 mg/m^2) of bendamustine would be as follows:

Treanda:
120 mg/m^2 x 1.7 m^2 (adult BSA) = 204 mg
Vials are 90 mg/mL
204 mg / 90 mg/mL= 2.3 mL
Each patient will receive 2.3 mL of 90 mg/mL strength

Based on the composition table above from the Applicant's NDA, 0.5 mL of Treanda contains 293 mg of DMA. So 2.3 mL will correspond to "**1.4 g**" of DMA.

Concentration of DMA in approved products:

Vumon
250 mg/m2 in children (~250 mg using 1 m^2 as the BSA)
50 mg/5mL ampule. Patients may receive up to five ampules.
DMA: 60 mg/mL or 300 mg/ampoule.
DMA per patient: 5 ampoules x 300 mg/ampule of DMA= **1500 mg (1.5 g) DMA**

2.5 Comments on Impurities/Degradants of Concern

Bendamustine propylene glycol esters ((b) (4) and (b) (4)) are formed due to esterification of the drug substance with propylene glycol during manufacturing of the drug product and upon storage. These impurities are not present in the currently marketed formulation of bendamustine drug product.

- The (b) (4)): a specification of not more than (NMT) (b) (4) % is proposed for the drug product.
- The (b) (4)): a specification of not more than (NMT) (b) (4) % is proposed for the drug product.

The proposed specifications for (b) (4) and (b) (4) are acceptable based on the results of the toxicology study conducted, indicating that the presence of the PGEs does not increase the toxicities associated with bendamustine.

2.6 Proposed Clinical Population and Dosing Regimen

Bendamustine is an alkylating drug indicated for treatment of patients with chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

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

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

2.7 Regulatory Background

Treanda® is marketed under two NDAs for treatment of CLL (NDA 22249) and indolent B-cell NHL after treatment with rituximab (NDA 22303).

3 Studies Submitted

3.1 Studies Reviewed

Study No.	Title	Module
Am-02-dp-2008-107	Evaluation of the Plasma Pharmacokinetics of Bendamustine Following Administration of Different Intravenous Formulations of CEP-18083 to Male Cynomolgus Monkeys.	4.2.2.7.
DS-2012-013	15-Week (Total of 5 Dose Cycles) Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study with CEP-18083 (Bendamustine) in Rats with a 4-Week Recovery Phase	4.2.3.2.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None referenced for this submission.

4 Pharmacology

Bendamustine is an alkylating drug with antineoplastic activity. See the label and original NDA review for additional information.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK\PD

Study Title: Evaluation of the Plasma Pharmacokinetics of Bendamustine Following Administration of Different Intravenous Formulations of CEP-18083 to Male Cynomolgus Monkeys

Report no.:	8201239
Study report location:	M4.2.3.7
Conducting laboratory and location:	(b) (4)
Date of study initiation:	24 February 2009
GLP compliance:	Yes
QA statement:	Yes
Test Article -1, and lot #, and purity	Treanda® Formulation, 25 mg vials, Lot # 08B27K, purity 95 to 105%
Test Article 2, and Lot # and purity:	CEP-18083 (the to be marketed formulation of Bendamustine), 90 mg/mL stock solution, Lot RYL-2711-154A, purity 99%
Test article 3, and Lot #:	100% DMA Formulation, 45 mg/mL stock solution, Lot RYL-2711-154B, purity 96%

Key Findings: Pharmacokinetic profiles of bendamustine and its two metabolites (M3 and M4) were similar in the 3 different Treanda formulations (1. Approved Treanda® formulation, 2. The to-be marked bendamustine formulation, 3. 100% DMA). See the table below for the details of study design excerpted from the Applicant's NDA.

Methods

Doses:	3 mg/kg of each formulations
Frequency of dosing:	Single bolus with 7 day washout period between three formulations
Route of administration:	Intravenous
Dose volume:	1 mL/kg
Formulation/Vehicle:	Sterile isotonic (0.9%) saline
Species/Strain:	Drug-naïve cynomolgous monkeys
Number/Sex/Group:	4 males
Age:	Young adults
Weight:	2.6 to 3.1 kg

Study design (excerpted from Applicant's NDA)

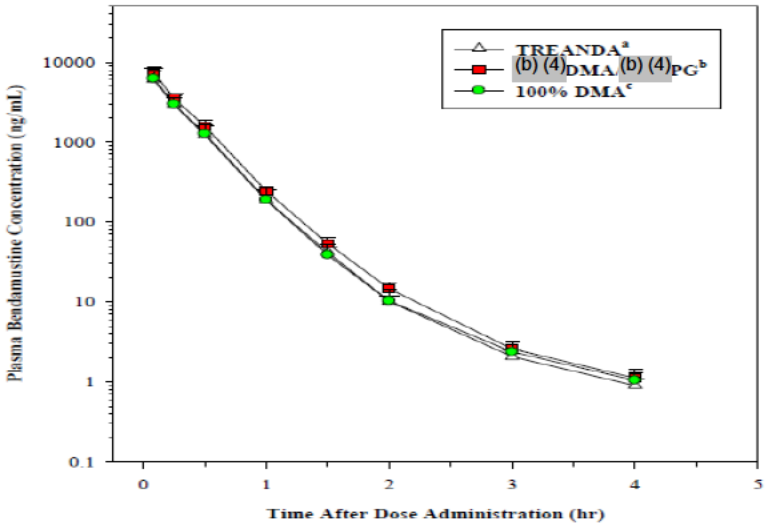
Phase[a]	No. of Males	Test Article	Dose Route	Formulation	Target Dose Level (mg/kg)	Target Dose Concentration (mg/mL)	Target Dose Volume (mL/kg)
1	4	CEP-18083	IV	TREANDA®[b]	3.0	3.0	1.0
2	4	CEP-18083	IV	(b) (4)DMA/(b) (4)PG[c]	3.0	3.0	1.0
3	4	CEP-18083	IV	100% DMA[d]	3.0	3.0	1.0

Group 1: the currently marketed formulation of bendamustine
Group 2: the to-be-marketed formulation of bendamustine
Group 3: bendamustine with DMA only (instead of DMA and PG which is proposed to be marketed)

Mean Pharmacokinetic Parameter Estimates after Intravenous Administration of Bendamustine Formulations to Male Cynomolgous Monkeys (excerpted from Applicant's NDA).

Formulation	Conc. (mg/mL)	C_{max} (ng/mL)	T_{max} (hours)	$T_{½}$ (hours)	$AUC_{0-\infty}$ (ng*hr/mL)
Treanda® for Injection	5	6037 ± 2456	0.083	0.57	2314 ± 800
100% N,N-dimethylacetamide	45	6209 ± 1300	0.083	0.63	2372 ± 535
(b) (4)N,N-dimethylacetamide /(b) (4) propylene glycol	90	7380 ± 1170	0.083	0.54	2854 ± 398

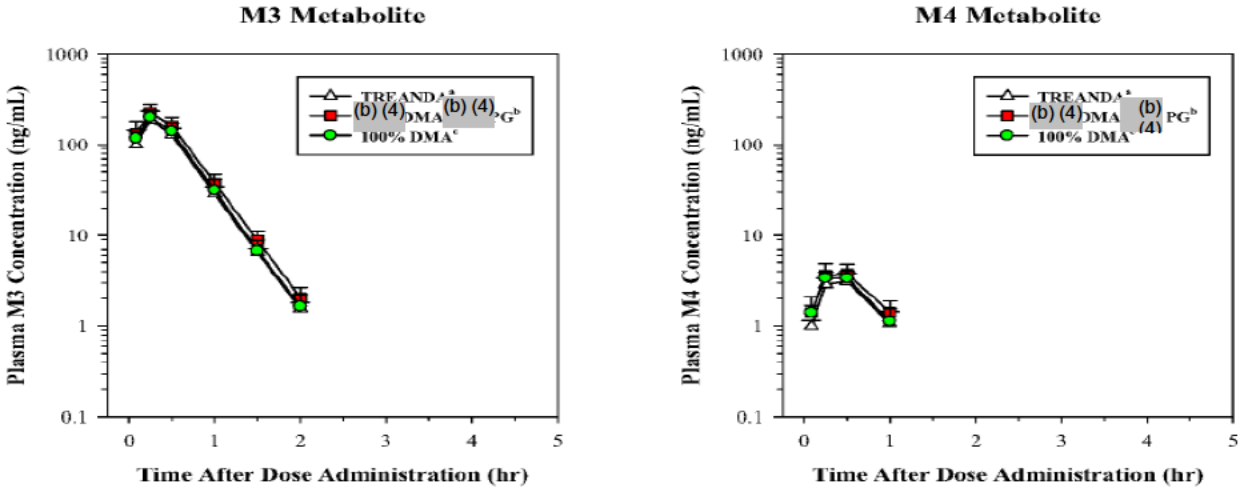
Plasma concentrations-vs.-time profiles of bendamustine in male Cynomolgous monkeys (N=3) administered single 3 mg/kg bolus intravenous doses of bendamustine in 3 different formulations (excerpted from Applicant's NDA).



[a]The dose formulation was prepared by constituting 25-mg vials of Treanda® with 0.9% NaCl.
[b]The dose formulation was prepared by diluting a 90-mg/mL stock solution of CEP-18083 in (b) (4) DMA/(b) (4) PG with 0.9% NaCl.

[c]The dose formulation was prepared by diluting a 45 mg/mL stock solution of CEP-18083 in 100% DMA with 09% NaCl.

Plasma concentrations-vs.-time profiles of M3 and M4 in male Cynomolgous monkeys (N=4) administered single 3 mg/kg bolus intravenous doses of bendamustine in 3 different formulations (excerpted from Applicant's NDA)



[a] The dose formulation was prepared by constituting 25-mg vials of Treanda® with 0.9% NaCl.
[b] The dose formulation was prepared by diluting a 90-mg/mL stock solution of CEP-18083 in (b) (4) DMA/ (b) (4) PG with 0.9% NaCl.
[c] The dose formulation was prepared by diluting a 45 mg/mL stock solution of CEP-18083 in 100% DMA with 09% NaCl.
Note: The values shown for the mean plasma concentrations of the M4 metabolite are overestimated by approximately 8%

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: 15-Week (Total of 5 Dose Cycles) Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study with CEP-18083 (Bendamustine) in Rats with a 4-Week Recovery Phase.

Introduction: The purpose of this study was to evaluate the toxicity and determine the toxicokinetics of the test article, CEP-18083 (the to-be-marketed formulation of bendamustine in (b) (4) DMA and (b) (4) PG), and to qualify the 2 propylene glycol esters ((b) (4) and (b) (4); 4:1 ratio) present in the drug product solution when administered over 5 dosing cycles.

Study no.:	8271137
Study report location:	M4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	20 August 2012
GLP compliance:	Yes
QA statement:	Yes
Drug lot #, and % purity:	CEP-18083 (the to-be-marketed formulation of bendamustine), Lot # 2F002B, purity 99.1% and Lot # 2F003B purity 99.6%. CEP-18083 solution is 90 mg/mL in (b) (4) DMA and (b) (4) PG
Propylene glycol ester mixture (PGE), Lot #, and purity:	(b) (4) 4:1 ratio, Lot # 3524-016, purity 101.1%; at (b) (4) total of each of the bendamustine HCl concentration.
Control Article:	Propylene glycol (PG) at (b) (4) and N,N-dimethylacetamide (DMA) at (b) (4) (Lot Nos. 3524-17 and 3524-25) Control article was diluted with sterile saline to the same dilution factor as the high dose of CEP-18083 (the to-be-marketed formulation of bendamustine).

Key Study Findings

- No remarkable differences in toxicities observed in the to-be-marketed formulation of bendamustine with or without PGEs.
- Mortality:
  - Deaths or unscheduled sacrifices due to moribundity occurred in all groups (1-5). The cause of death was considered as combination of chronic catheterization associated with inflammatory response, as well as related to blood collection.
- Target organs
  - Kidney: this was the main toxicity in all groups and included renal tubular degeneration/necrosis, karyomegaly/cytomegaly, chronic progressive nephropathy and mononuclear cell infiltrates
  - Other organs/ tissues: brain, heart, liver, and lung (mononuclear cell infiltration), heart (degenerative cardiomyopathy), bone marrow/hematopoietic system (↓ blood cells), femur and liver (hyperplasia); ↓ in epididymis weight.
- Systemic exposure to bendamustine and 2 circulating metabolites (M3 and M4) were generally dose-related and comparable with or without PGEs over the

range evaluated on all sampling days. The metabolites were present at much lower concentrations than the parent compound, bendamustine. The $t_{1/2}$ values ranged from 0.5 to 1 hr.

Methods

Doses:	Groups 2-5: 5, 10, and 15 mg/kg of bendamustine Groups 2, 3, and 4 also contained 0.5, 1, or 1.5 mg/kg of PGE, respectively.
Frequency of dosing:	Once daily for 3 consecutive days followed by 18 days without test article infusion (21-day cycle).
Route of administration:	Intravenous infusion via a catheter implanted in a femoral vein
Dose volume:	10 mL/kg over 30 minutes
Formulation/Vehicle:	Sterile isotonic (0.9%) saline
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	20
Age:	8 to 9 weeks old
Weight:	244 to 341 g for the males 191 to 265 g for the females
Satellite groups:	3/sex/group 1 (control) and 9/sex groups 2-5 (test article treatment)
Unique study design:	There is no vehicle control group with sterile isotonic (0.9%) saline (see group designation table excerpted from the Applicant's NDA).
Deviation from study protocol:	There were 8 protocol deviations and 1 planned deviation. The Study Director concluded that there is no impact on overall interpretation or integrity of the study due to these deviations.

Group	Subgroup[a,b]	No. of Animals Male	No. of Animals Female	Dose Level RTU (mg/kg/dose)	Dose Concentration RTU (mg/mL)	Dose Level PGE (mg/kg/dose)	Dose Concentration PGE (mg/mL)
1 (Control)[c]	1 (Toxicity)	20	20	0	0	0	0
	2 (Toxicokinetic)	3	3	0	0	0	0
2 (Low- RTU + PGE)[d]	1 (Toxicity)	20	20	5	0.5	0.5	0.05
	2 (Toxicokinetic)	9	9	5	0.5	0.5	0.05
3 (Mid- RTU + PGE)[d]	1 (Toxicity)	20	20	10	1.0	1.0	0.1
	2 (Toxicokinetic)	9	9	10	1.0	1.0	0.1
4 (High- RTU + PGE)[d]	1 (Toxicity)	20	20	15	1.5	1.5	0.15
	2 (Toxicokinetic)	9	9	15	1.5	1.5	0.15
5 (High- RTU)[e]	1 (Toxicity)	20	20	15	1.5	0	0
	2 (Toxicokinetic)	9	9	15	1.5	0	0

PGE = Propylene glycol esters of bendamustine; RTU = Bendamustine hydrochloride solution.
a Toxicity animals designated for recovery sacrifice (up to 5 animals/sex/group, depending on survival) underwent 4 weeks of recovery following dose administration.
b Toxicokinetic animals were included solely for the purpose of blood sample collections.
c Group 1 received control article diluted with sterile saline to the same dilution factor as the high dose of Test Article 1.
d Groups 2, 3, and 4 received Test Article 1 and Test Article 2 administered as a co-formulation in diluent (sterile saline).
e Group 5 received Test Article 1 only in diluent (sterile saline).

RTU: Ready-to-use (refers to the to-be-marketed formulation containing (b) (4) DMA and (b) (4) PG)

Observations and Results

Mortality:	Twice daily
Clinical signs:	Twice daily
Body weights:	Weekly
Food consumption:	Weekly
Ophthalmoscopy:	Pre-dose and on Days 102 for females and 103 for males
Hematology:	Day 4, 25, 46, 67, 88, and terminal sacrifice
Clinical chemistry:	Day 4, 46, 88, and terminal sacrifice
Urinalysis:	Day 46, 88, and terminal sacrifice
Coagulation:	Day 46, 88, and terminal sacrifice
Gross pathology:	Terminal sacrifice
Organ weights:	Terminal sacrifice
Histopathology:	Terminal sacrifice
Bioanalytical analysis	Dosing Day 1, 3, 85, 87

Mortality

Animals that were moribund or found dead had swollen thorax and inguinal areas. Hematology changes in most animals included a decrease in absolute reticulocyte count, lymphocyte count, leukocytes. Tissues were not collected from animals found dead or moribund animals.

Test Article	mg/kg	Phase/group	Day	Sex	Fate Status
Control article	0	Dosing/Toxicity	59	F	Moribund
Control article	0	Dosing/Toxicity	67	F	Moribund
Control article	0	Dosing/Toxicity	46	F	Accidental death
Bendamustine HCl + PGE	5 + 0.5	Dosing/Toxicity	35	M	Moribund
Bendamustine HCl + PGE	5 +0.5	Dosing/Toxicity	55	M	Other
Bendamustine HCl + PGE	5 +0.5	Dosing/Toxicity	56	M	Found dead
Bendamustine HCl + PGE	5 +0.5	Dosing/Toxicity	30	M	Other
Bendamustine HCl + PGE	5 +0.5	Dosing/TK	23	M	Moribund
Bendamustine HCl + PGE	5 +0.5	Dosing/Toxicity	32	F	Moribund
Bendamustine HCl + PGE	5 +0.5	Dosing/Toxicity	41	F	Moribund
Bendamustine HCl + PGE	5 +0.5	Dosing/Toxicity	46	F	Accidental
Bendamustine HCl + PGE	5 +0.5	Dosing/TK	45	F	Moribund
Bendamustine	10+1.0	Dosing/Toxicity	35	M	Moribund

Test Article	mg/kg	Phase/group	Day	Sex	Fate Status
HCl + PGE					
Bendamustine HCl + PGE	10 +1.0	Dosing/Toxicity	60	M	Moribund
Bendamustine HCl + PGE	10 +1.0	Dosing/Toxicity	75	M	Moribund
Bendamustine HCl + PGE	10 +1.0	Dosing/Toxicity	71	M	Moribund
Bendamustine HCl + PGE	10 +1.0	Dosing/Toxicity	30	M	Moribund
Bendamustine HCl + PGE	10 +1.0	Dosing/Toxicity	30	M	Moribund
Bendamustine HCl + PGE	10 +1.0	Dosing/Toxicity	53	M	Moribund
Bendamustine HCl + PGE	10+1.0	Dosing/Toxicity	23	F	Found dead
Bendamustine HCl + PGE	10+1.0	Dosing/Toxicity	27	F	Moribund
Bendamustine HCl + PGE	10+1.0	Dosing/Toxicity	69	F	Moribund
Bendamustine HCl + PGE	10+1.0	Dosing/Toxicity	31	F	Other
Bendamustine HCl + PGE	15+1.5	Dosing/Toxicity	71	M	Moribund
Bendamustine HCl + PGE	15+1.5	Dosing/Toxicity	72	M	Other
Bendamustine HCl + PGE	15+1.5	Dosing/Toxicity	60	M	Moribund
Bendamustine HCl + PGE	15+1.5	Dosing/Toxicity	41	M	Found dead
Bendamustine HCl + PGE	15+1.5	Dosing/Toxicity	86	F	Found dead
Bendamustine HCl + PGE	15+1.5	Dosing/TK	58	F	Moribund
Bendamustine HCl	15*	Dosing/Toxicity	90	M	Moribund
Bendamustine HCl	15*	Dosing/Toxicity	64	F	Found dead
Bendamustine HCl	15*	Dosing/Toxicity	72	F	Found dead

Clinical Signs

Malocclusions in males given 15 mg/kg/dose bendamustine with or without PGE and missing teeth in two males given 15 mg/kg/dose bendamustine alone were noted.

Bendamustine + PGE						
Dose in mg/kg		**0**	**5+0.5**	**10+1.0**	**15+1.5**	**15***
No. of animals		**20**	**20**	**20**	**20**	**20**
Observations		**No. of animals affected - Males**				
Appearance	limited use, hind legs	**0**	**1**	**1**	0	0
	Malocclusion	0	0	0	6	5

Bendamustine + PGE						
Dose in mg/kg		**0**	**5+0.5**	**10+1.0**	**15+1.5**	**15***
No. of animals		**20**	**20**	**20**	**20**	**20**
Observations		**No. of animals affected - Males**				
	missing, teeth	0	0	0	0	2
	swollen, dorsal thorax	0	0	2	0	0
	swollen, left dorsal thorax	0	1	3	1	
	swollen, left inguinal	0	1	0	0	0
Behavior	animal leapt from cage	0	1	0	0	0
	hypoactive	0	1	0	0	0
	recumbent, sternal	0	0	0	1	
Discharge	genital, red	1	0	0	0	1
Excretion	feces, nonformed	0	0	0	0	1
	urine, discolored, red	0	0	0	0	1
Eyes	discharge, right eye, red	1	0	0	0	1
Respiration	labored	0	0	0	1	0
Skin and pelage	alopecia, front feet	0	0	1	0	0
	alopecia, front legs	0	0	1	0	0
	cold to touch, entire body	0	0	0	1	0
	discolored haircoat, nose, red	0	1	0	0	0
	discolored haircoat, perineal, yellow	0	1	0	0	0
	discolored skin, hind feet, purple	0	0	1	0	0
	rough haircoat	1	0	0	0	1
	scab, dorsal thorax	1	0	0	0	
	scab, left inguinal scab, left shoulder	0	0	1	0	0
	scab, nose	0	1	0	0	0
	scab, right shoulder	1	0	0	0	0
	sore, dorsal thorax	1	0	2	0	1
	sore, left cervical	1	0	0	0	0
	sore, left inguinal	0	0	1	0	0
	skin and pelage sore, left shoulder	0	0	1	0	0
	sore, midline cervical	0	0	1	0	0
	sore, right shoulder	1	0	0	0	0

*Bendamustine alone

Bendamustine + PGE						
Dose in mg/kg		**0**	**5+0.5**	**10+1.0**	**15+1.5**	**15***
No. of animals		**20**	**20**	**20**	**20**	**20**
Observations		**No. of animals affected - Females**				
Appearance	limited use, right hind leg	0	0	1	0	0
	swollen, entire head	0	0	0	0	1
	swollen, hind feet	0	0	0	1	0
	swollen, left abdomen	0	0	0	1	0
	swollen, left inguinal	0	0	0	3	2

Bendamustine + PGE						
Dose in mg/kg		**0**	**5+0.5**	**10+1.0**	**15+1.5**	**15***
No. of animals		**20**	**20**	**20**	**20**	**20**
Observations		**No. of animals affected - Females**				
	swollen, perioral	0	0	0	0	1
	swollen, left shoulder	0	1	0	0	0
	swollen, left ventral thorax	0	1	0	0	0
Behavior	animal struggled excessively, during sample collection	0	0	0	0	1
Discharge	nasal, red	0	0	1	0	0
	oral, clear	0	0	0	1	1
	oral, red	0	0	0	0	1
	red, dorsal cervical	0	0	1	0	
Eyes	opaque, right eye	0	0	0	0	1
Skin and pelage	alopecia, front legs	1	1	0	0	
	discolored haircoat, perioral, red	0	0	0	0	1
	rough haircoat	0	0	0	0	1
	scab, front legs	1	0	0	0	0
	scab, left side head	0	0	0	1	0
	scab, right front leg	1	0	0	0	0
	sore, left side head	0	0	0	0	1
	thinning hair coat, front feet	0	0	1	1	1
	thinning hair coat, front legs	1	1	0	0	0
	thinning hair coat, left abdomen	0	0	0	0	1
	thinning hair coat, midline abdomen	0	0	0	0	2
	thinning hair coat, right abdomen	0	0	1	0	0

*Bendamustine alone

Body Weights
Unremarkable

Food Consumption
Unremarkable

Ophthalmoscopy
Unremarkable

Hematology
Blood samples were collected on Day 4, 25, 46, 67, 88 and 106 during the dosing phase. Changes in hematology included decreases in the reticulocytes, platelets, WBC count, lymphocytes, leukocytes, eosinophils, and basophils during the dosing period (pancytopenia).

Bendamustine + PGE mg/kg	Reticulocytes						Platelets					
	Males			Females			Males			Females		
	D4	D88	D106	D4	D88	D106	D4	D88	D106	D4	D88	D106
5+0.5	-9	-20*	11	-16*	3	18	-	-	8	-	-	7
10+1.0	-19*	-38*	0	-25*	-26*	18	-	-	16	-	-	9
15+1.5	-27*	-39*	11	-40*	-34*	31	-	-	21*	-	-	20*
15‡	-15*	-49*	8	-32*	-32	10	-	-	23*	-	-	18*

* Statistically significant compared to control group ((b) (4) PG and (b) (4) DMA).
-: no finding/ no toxicologically significant finding.
‡ Bendamustine alone

Bendamustine + PGE mg/kg	WBC						Neutrophils					
	Males			Females			Males			Females		
	D4	D88	D106	D4	D88	D106	D4	D88	D106	D4	D88	D106
5+0.5	-51*	49*	176	-22	3	-6	-52*	140	722	-	-	-
10+1.0	-58*	-43*	-16	-57*	-39*	-12	-24*	2	66	-	-	-
15+1.5	-77*	-68*	-25*	-66*	-27	2	-68*	-53*	-5	-	-	-
15‡	-75*	-62*	-19	-61*	-43*	-4	-64*	-37*	36	-	-	-

* Statistically significant compared to control group ((b) (4) PG and (b) (4) DMA).
-: no finding/ no toxicologically significant finding.
‡ Bendamustine alone

Bendamustine + PGE mg/kg	Lymphocytes						Basophils					
	Males			Females			Males			Females		
	D4	D88	D106	D4	D88	D106	D4	D88	D106	D4	D88	D106
5+0.5	-51*	-39*	-18	-27*	-38*	-16	-60*	-50*	-33	-50*	-29	0
10+1.0	-70*	-68*	-40*	-58*	-64*	-20	-80*	-75*	0	-50*	-43*	0
15+1.5	-82*	-80*	-348	-75*	-67*	-24	-80*	-75*	-33	-100	-43*	0
15‡	-80*	-79*	-36*	-69*	-63*	-9	-80*	-75*	0	-100*	-43*	0

* Statistically significant compared to control group ((b) (4) PG and (b) (4) DMA).
-: no finding/ no toxicologically significant finding.
‡ Bendamustine alone

Bendamustine + PGE mg/kg	Leukocytes						Eosinophils					
	Males			Females			Males			Females		
	D4	D88	D106	D4	D88	D106	D4	D88	D106	D4	D88	D106
5+0.5	-67**	-	-	-	-17	-	-43*	-25*	94	-37	-	-
10+1.0	-33*	-	-	-	-50*	-	-57*	-25	6	-42	-	-
15+1.5	-83*	-	-	-	-67*	-	-57*	-19	19	-63*	-	-
15‡	-83*	-	-	-	-50*	-	-36*	-38*	13	-47*	-	-

* Statistically significant compared to control group ((b) (4) PG and (b) (4) DMA).
-: no finding/ no toxicologically significant finding.
‡ Bendamustine alone

Clinical Chemistry

Bendamustine + PGE mg/kg	ALT						Phosphorous					
	Males			Females			Males			Females		
	D4	D88	D106	D4	D88	D106	D4	D88	D106	D4	D88	D106
5+0.5	-26*	-26*	-23				2	9*	8	0	13	-2
10+1.0	-30*	21*	33				2	6*	3	1	15	2
15+1.5	-33*	-23*	-23				9*	12*	6	1	28*	6
15‡	-30*	-26*	-26				5	4	5	-1	13	4

* Statistically significant compared to control group ((b) (4) PG and (b) (4) DMA).
-: no finding/ no toxicologically significant finding.
‡ Bendamustine alone

Bendamustine + PGE mg/kg	Sodium						Potassium					
	Males			Females			Males			Females		
	D4	D88	D106	D4	D88	D106	D4	D88	D106	D4	D88	D106
5+0.5	0	1*	0	1	1	0	0	11*	7*	0	7	2
10+1.0	0	1	0	1*	1	0	-4	2	-3	-2	9*	0
15+1.5	1*	1*	0	0	1	-1	2	11*	2	4	11*	4
15‡	-1	0	0	0	0	-1	-5	0	-5	0	7	2

* Statistically significant compared to control group ((b) (4) PG and (b) (4) DMA).
-: no finding/ no toxicologically significant finding.
‡ Bendamustine alone

Urinalysis

Granular casts were observed in the urine sediment of males and females given 15 mg/kg/dose CEP-18083 + 1.5 mg/kg/dose PGE and 15 mg/kg/dose CEP-18083 alone on day 46.

Coagulation

Unremarkable

Gross Pathology

Macroscopic Findings		No. of animals affected									
Bendamustine (mg/kg)		0	5	10	15	15	0	5	10	15	15
PGE (mg/kg)		0	0.5	1.0	1.5	0	0	0.5	1.0	1.5	0
Number of animals examined		15	11	10	11	14	12	12	11	14	13
Organ	Finding	Males					Females				
Kidney	Adhesion	0	0	0	0	0	0	0	0	1	0
	Large	0	1	2	0	1	0	0	0	1	0
	Raised area	0	0	0	0	0	0	0	0	1	0
Liver	Discolored	0	0	0	0	0	0	0	2	0	0
	Raised area	0	0	0	1	0	0	0	0	0	0
Lung	Discolored	0	0	0	0	1	0	0	0	0	0

Macroscopic Findings		No. of animals affected									
Bendamustine (mg/kg)		0	5	10	15	15	0	5	10	15	15
PGE (mg/kg)		0	0.5	1.0	1.5	0	0	0.5	1.0	1.5	0
Number of animals examined		15	11	10	11	14	12	12	11	14	13
Organ	Finding	Males					Females				
Lymph Node, Mandibular	Discolored	0	1	0	0	0	0	0	0	0	0
Marrow, Femur	Discolored	0	1	0	0	0	0	0	0	0	0
Pancreas	Adhesion	0	0	0	0	1	0	0	0	0	0
Seminal Vesicle	Small	0	0	0	0	1	NA	NA	NA	NA	NA
Skin/Subcutis	Alopecia	0	0	0	0	0	0	0	1	1	0
	Sore	1	0	1	0	1	0	0	0	0	0
Spleen	Large	0	1	1	0	0	0	0	0	1	0
Stomach	Discolored	0	0	0	0	0	0	1	0	0	0
Ureter	Large	0	0	0	0	1	0	0	0	0	0
Urinary Bladder	Adhesion	0	0	0	0	1	0	0	0	0	0
	Calculus	0	1	0	0	1	0	0	0	0	0
	Discolored	0	1	0	0	0	0	0	0	0	0
	Large	0	1	0	0	1	0	0	0	0	0
	Thickened	0	1	0	0	1	0	0	0	0	0
Uterus	Constricted	NA	NA	NA	NA	NA	0	0	0	1	0

NA = Not Applicable, tissue does not exist in this sex

Organ Weights

Males

Group and Dose		Mean	Percentage deviation from Control			
Bendamustine + PGE		Control 0 mg/kg	5 +1.5 mg/kg	10+1.0 mg/kg	15+1.5 mg/kg	15 mg/kg
Necropsy		Terminal	Terminal	Terminal	Terminal	Terminal
Number of animals examined		15	11	10	11	14
Epididymides	Absolute (g)	1.67	-13*	-15*	-17*	-11*
	Relative	0.275	-11	-12	-10	-5

Group and Dose		Mean	Percentage deviation from Control			
Bendamustine + PGE		Control 0 mg/kg	5 +1.5 mg/kg	10+1.0 mg/kg	15+1.5 mg/kg	15 mg/kg
Necropsy		Terminal	Terminal	Terminal	Terminal	Terminal
Number of animals examined		15	11	10	11	14
	BW (%)					
Seminal Vesicle	Absolute (g)	2.09	-2	-18*	-15	-3
	Relative BW (%)	0.736	-52	-60	-56	-52

Females: Unremarkable

Histopathology

Adequate Battery: Yes

Peer Review: Yes, for kidney only

Renal tubular degeneration/necrosis and/or karyomegaly/cytomegaly were observed in males and females given bendamustine with or without PGE. Chronic progressive nephropathy and mononuclear cell infiltrates were observed in males and females given bendamustine with or without PGE and in control article group. An increased incidence in mononuclear cell infiltrates was noted in females given 15 mg/kg/dose CEP-18083 + 1.5 mg/kg/dose PGE.

Histological Findings

Treatment-Related Microscopic Findings		No. of animals affected									
Bendamustine (mg/kg)		0	5	10	15	15	0	5	10	15	15
PGE (mg/kg)		0	0.5	1.0	1.5	0	0	0.5	1.0	1.5	0
Number of animals examined		15	11	10	11	14	12	12	11	14	13
Organ	Finding	Males					Females				
Catheter Site	Edema	0	1	0	1	1	0	0	0	1	0
	Fibrosis	11	5	3	5	3	10	12	10	13	8
	Hemorrhage	0	1	1	1	0	1	0	0	0	1
	Inflammation	0	1	1	1	1	2	4	5	4	4
	Intima, thickened	9	6	7	8	13	1	3	2	1	2
	Mineralization	0	0	0	0	0	3	2	1	7	3
	Pigment	1	1	0	1	1	2	1	3	6	4
	Thrombus	1	0	0	3	1	3	2	3	5	0
Infusion Site	Fibrosis	9	4	7	3	14	8	9	8	12	12
	Hemorrhage	0	0	0	0	1	0	1	0	0	0
	Inflammation	1	0	2	3	4	0	2	1	1	2

Treatment-Related Microscopic Findings		No. of animals affected									
Bendamustine (mg/kg)		0	5	10	15	15	0	5	10	15	15
PGE (mg/kg)		0	0.5	1.0	1.5	0	0	0.5	1.0	1.5	0
Number of animals examined		15	11	10	11	14	12	12	11	14	13
Organ	Finding	Males					Females				
	Intima, thickened	3	7	4	3	0	1	2	2	0	1
	Mineralization	4	4	0	0	2	1	1	2	1	1
	Pigment	0	3	0	0	5	1	0	2	1	3
	Thrombus	7	4	2	1	6	1	3	5	4	4
	C-Hematopoietic neoplasm, see body, whole for type	0	1	0	0	0	0	0	0	0	0
Brain	Infiltrate, mononuclear cell, choroid plexus	0	0	0	0	1	0	0	0	0	0
Body	M-Leukemia, granulocytic	0	1	2	0	0	0	0	0	0	0
Heart	Cardiomyopathy, degenerative	5	0	0	7	3	0	0	0	0	0
	Infiltrate, mononuclear cell	3	0	0	0	3	0	0	0	1	3
	Inflammation, macrophages	0	0	0	0	1	0	0	0	0	0
Kidney	B-Adenoma, tubule cell, amphophilic-vacuolar	0	0	1	0	0	0	0	0	1	0
	Cast, proteinaceous	0	0	0	1	1	0	1	1	2	2
	C-Hematopoietic neoplasm, see body, whole for type	0	1	0	0	0	0	0	0	0	0
	Degeneration/necrosis, tubule	0	0	9	10	13	0	0	4	11	8
	Dilation pelvis	0	0	1	0	0	0	0	0	0	0
	Dilatation, tubule(s)	1	0	1	0	0	1	0	0	1	0
	Fibrosis	0	0	0	0	1	0	1	0	1	2
	Hyaline droplet, tubule cell Pyelonephritis	0	2	0	0	0	0	0	0	1	0
	Hyperplasia, atypical, tubule cell	0	1	1	0	0	0	1	0	2	0
	Infiltrate, mononuclear cell	5	3	4	9	13	1	4	2	8	3
	Karyomegaly/cytomegaly, tubule cell	0	2	9	10	14	0	0	11	14	11
	Mineralization, tubule	0	0	0	0	0	1	4	4	8	6
	Nephropathy, chronic progressive	8	6	7	8	11	1	2	1	0	4
	Pyelonephritis	0	1	1	0	1	0	1	0	1	0
Liver	Hepatodiaphragmatic nodule	0	0	0	1	0	0	0	0	0	0
	Hyperplasia, bile duct	0	0	0	0	0	0	0	0	0	1
	Infiltrate, mononuclear cell	7	0	0	5	6	5	0	0	5	6
	Inflammation, capsule	0	0	0	0	0	0	0	0	1	0
	Inflammation/Necrosis	0	0	0	0	0	0	0	0	0	1
	Necrosis	2	0	0	0	0	0	0	0	1	1
	Vacuolation, macrovesicular,hepatocyte	2	0	0	2	2	1	0	0	1	1
	Vacuolation, microvesicular,hepatocyte	2	0	0	1	1	0	0	0	1	0
Lung	Infiltrate, macrophages, alveolus	1	0	0	0	0	0	0	0	0	1
	Infiltrate, mononuclear cell	0	0	0	0	0	0	0	0	1	1

Treatment-Related Microscopic Findings		No. of animals affected									
Bendamustine (mg/kg)		0	5	10	15	15	0	5	10	15	15
PGE (mg/kg)		0	0.5	1.0	1.5	0	0	0.5	1.0	1.5	0
Number of animals examined		15	11	10	11	14	12	12	11	14	13
Organ	Finding	Males					Females				
	Pigment	0	0	0	0	0	0	0	0	0	1
	Thrombus	0	0	0	0	0	1	0	0	1	0
Lymph Node, Mandibular	C-Hematopoietic neoplasm, see body, whole for type	0	1	0	0	0	0	0	0	0	0
	Lymphocytes, decreased	0	0	0	0	1	0	0	0	0	0
	Macrophages, increased	0	0	0	2	0	0	0	0	0	0
Lymph Node, Mesenteric	Necrosis, lymphocytes	0	0	0	0	1	0	0	0	0	0
	Pigment	0	0	0	1	2	0	0	0	0	0
Marrow, Femur	Hyperplasia, myeloid	0	0	0	0	0	0	0	0	1	0
	C-Hematopoietic neoplasm, see body, whole for type	0	1	0	0	0	0	0	0	0	0
	Necrosis	0	1	0	0	0	0	0	0	0	0
Ovary	Cyst, corpus luteum	NA	NA	NA	NA	NA	0	0	0	1	0
	Cyst, follicle, increased	NA	NA	NA	NA	NA	1	0	0	0	1
	Involution/decreased corpora lutea	NA	NA	NA	NA	NA	6	0	0	6	4
Spleen	Hematopoiesis, extramedullary,decreased	0	0	0	0	1	0	0	0	0	0
	Infiltrate, plasma cells	0	0	0	0	0	0	0	0	1	0
	Lymphocytes, decreased	0	0	0	0	1	0	0	0	0	0
Testis	Infiltrate, mononuclear cell, interstitium	1	0	0	0	0	0	0	0	0	0
	Syncytial cell	0	0	0	0	1	0	0	0	0	0

Bioanalytical analysis

Systemic exposure to bendamustine and two circulating metabolites, M3 and M4, are presented in the Tables below (excerpted from the Applicants NDA).

- Systemic exposure to bendamustine and 2 circulating metabolites (M3 and M4) were generally dose-related and comparable with or without PGEs over the range evaluated on all sampling days.
- The metabolites were present at much lower concentrations than the parent bendamustine.
- The systemic exposure to bendamustine and 2 circulating metabolites (M3 and M4) did not appear to differ with respect to the sex of the animal or the day of dosing (Day 1 to Day 87). The $t_{1/2}$ values ranged from 0.5 to 1 hr.

Composite toxicokinetic parameters for bendamustine in male and female rats on the first and last day of cycles 1 (Days 1 and 3) and 5 (Days 85 and 87) of intermittent infusion of bendamustine + PGE or bendamustine only for 15 weeks (total 5 dose cycles)

Sex	Day	Group	Treatment	RTU Dose (mg/kg/day)	PGE Dose (mg/kg/day)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng•hr/mL)
Male	1	2	RTU + PGE	5	0.5	3399	0.5	1901
		3	RTU + PGE	10	1.0	7184	0.5	4375
		4	RTU + PGE	15	1.5	10522	0.5	7063
		5	RTU	15	0	10365	0.5	6610
	3	2	RTU + PGE	5	0.5	3702	0.5	2040
		3	RTU + PGE	10	1.0	9705	0.5	5611
		4	RTU + PGE	15	1.5	10122	0.5	8220
		5	RTU	15	0	7178	0.5	4905
	85	2	RTU + PGE	5	0.5	3278	0.5	1889
		3	RTU + PGE	10	1.0	7151	0.5	4660
		4	RTU + PGE	15	1.5	13204	0.5	8116
		5	RTU	15	0	11179	0.5	6561
	87	2	RTU + PGE	5	0.5	4900	0.5	2633
		3	RTU + PGE	10	1.0	12917	0.5	7211
		4	RTU + PGE	15	1.5	16677	0.5	9978
		5	RTU	15	0	12219	0.5	7097
Female	1	2	RTU + PGE	5	0.5	2665	0.5	1786
		3	RTU + PGE	10	1.0	2693	0.5	1812
		4	RTU + PGE	15	1.5	6058	0.5	4141
		5	RTU	15	0	6749	0.5	4081
	3	2	RTU + PGE	5	0.5	2169	0.5	1430
		3	RTU + PGE	10	1.0	4144	0.5	2499
		4	RTU + PGE	15	1.5	9089	0.5	5183
		5	RTU	15	0	7369	0.5	5420
	85	2	RTU + PGE	5	0.5	3846	0.5	2037
		3	RTU + PGE	10	1.0	5483	0.5	3261
		4	RTU + PGE	15	1.5	9873	0.5	5771
		5	RTU	15	0	12565	0.5	7406
	87	2	RTU + PGE	5	0.5	2928	0.5	1577
		3	RTU + PGE	10	1.0	4417	0.5	2582
		4	RTU + PGE	15	1.5	8441	0.5	4911
		5	RTU	15	0	8377	0.5	4756

RTU: Non-aqueous ready-to-use bendamustine HCl solution. PGE: Propylene glycol esters of bendamustine.

Composite toxicokinetic parameters for M3 metabolite in male and female rats on the first and last day of cycles 1 (Days 1 and 3) and 5 (Days 85 and 87) of intermittent infusion of bendamustine + PGE or bendamustine only for 15 weeks (total 5 dose cycles)

Sex	Day	Group	Treatment	RTU Dose (mg/kg/day)	PGE Dose (mg/kg/day)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng•hr/mL)
Male	1	2	RTU + PGE	5	0.5	130.62	0.5	82.5
		3	RTU + PGE	10	1.0	146.50	1.0	175.7
		4	RTU + PGE	15	1.5	159.61	0.5	190.7
		5	RTU	15	0	199.49	0.5	193.7
	3	2	RTU + PGE	5	0.5	96.86	0.5	58.9
		3	RTU + PGE	10	1.0	112.86	1.0	138.9
		4	RTU + PGE	15	1.5	133.20	0.5	171.2
		5	RTU	15	0	157.11	0.5	157.7
	85	2	RTU + PGE	5	0.5	48.50	0.5	27.3
		3	RTU + PGE	10	1.0	69.53	1.0	67.7
		4	RTU + PGE	15	1.5	57.86	0.5	79.3
		5	RTU	15	0	76.15	1.0	91.3
	87	2	RTU + PGE	5	0.5	41.54	0.5	22.9
		3	RTU + PGE	10	1.0	36.66	1.0	22.2
		4	RTU + PGE	15	1.5	53.28	0.5	61.3
		5	RTU	15	0	57.59	0.5	63.6
Female	1	2	RTU + PGE	5	0.5	118.24	0.5	81.3
		3	RTU + PGE	10	1.0	102.84	0.5	87.5
		4	RTU + PGE	15	1.5	161.01	0.5	135.1
		5	RTU	15	0	231.41	0.5	156.7
	3	2	RTU + PGE	5	0.5	112.27	0.5	65.4
		3	RTU + PGE	10	1.0	69.44	0.5	54.3
		4	RTU + PGE	15	1.5	128.80	0.5	97.4
		5	RTU	15	0	177.63	0.5	120.6
	85	2	RTU + PGE	5	0.5	78.72	0.5	42.0
		3	RTU + PGE	10	1.0	92.94	0.5	70.3
		4	RTU + PGE	15	1.5	156.26	0.5	120.4
		5	RTU	15	0	322.50	0.5	185.1
	87	2	RTU + PGE	5	0.5	60.46	0.5	32.1
		3	RTU + PGE	10	1.0	51.59	0.5	41.4
		4	RTU + PGE	15	1.5	127.92	0.5	88.1
		5	RTU	15	0	165.63	0.5	96.1

RTU: Non-aqueous ready-to-use bendamustine HCl solution. PGE: Propylene glycol esters of bendamustine.

Composite toxicokinetic parameters for M4 metabolite in male and female rats on the first and last day of cycles 1 (Days 1 and 3) and 5 (Days 85 and 87) of intermittent infusion of bendamustine + PGE or bendamustine only for 15 weeks (total 5 dose cycles**)**

Sex	Day	Group	Treatment	RTU Dose (mg/kg/day)	PGE Dose (mg/kg/day)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng•hr/mL)
Male	1	2	RTU + PGE	5	0.5	2.91	0.5	0.7
		3	RTU + PGE	10	1.0	3.79	0.5	2.3
		4	RTU + PGE	15	1.5	5.32	0.5	3.1
		5	RTU	15	0	5.01	0.5	3.0
	3	2	RTU + PGE	5	0.5	2.59	0.5	0.6
		3	RTU + PGE	10	1.0	3.92	0.5	2.3
		4	RTU + PGE	15	1.5	4.63	0.5	2.8
		5	RTU	15	0	4.04	0.5	2.5
	85	2	RTU + PGE	5	0.5	1.23	0.5	0.3
		3	RTU + PGE	10	1.0	1.42	1.0	1.1
		4	RTU + PGE	15	1.5	3.00	0.5	1.9
		5	RTU	15	0	2.28	0.5	1.6
	87	2	RTU + PGE	5	0.5	1.06	0.5	0.3
		3	RTU + PGE	10	1.0	1.39	0.5	0.9
		4	RTU + PGE	15	1.5	2.57	0.5	1.6
		5	RTU	15	0	2.33	0.5	0.6
Female	1	2	RTU + PGE	5	0.5	2.21	0.5	0.6
		3	RTU + PGE	10	1.0	3.31	0.5	0.8
		4	RTU + PGE	15	1.5	5.46	0.5	3.1
		5	RTU	15	0	6.21	0.5	4.2
	3	2	RTU + PGE	5	0.5	2.10	0.5	0.5
		3	RTU + PGE	10	1.0	1.93	0.5	0.5
		4	RTU + PGE	15	1.5	5.19	0.5	2.9
		5	RTU	15	0	5.03	0.5	1.3
	85	2	RTU + PGE	5	0.5	3.66	0.5	0.9
		3	RTU + PGE	10	1.0	5.20	0.5	2.9
		4	RTU + PGE	15	1.5	7.53	0.5	4.3
		5	RTU	15	0	11.92	0.5	6.3
	87	2	RTU + PGE	5	0.5	2.49	0.5	0.6
		3	RTU + PGE	10	1.0	1.89	0.5	0.5
		4	RTU + PGE	15	1.5	5.87	0.5	1.5
		5	RTU	15	0	5.49	0.5	1.4

RTU: Non-aqueous ready-to-use bendamustine HCl solution. PGE: Propylene glycol esters of bendamustine.

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/s/

RAMADEVI GUDI
06/17/2013

HALEH SABER
06/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

06 June 2013

NDA: 22249/S015

Drug Product Name
Proprietary: TREANDA
Non-proprietary: bendamustine hydrochloride

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
08 MAR 2013	08 MAR 2013	02 MAY 2013	03 MAY 2013
21 MAY 2013	21 MAY 2013	N/A	N/A
03 JUN 2013	03 JUN 2013	N/A	N/A

Applicant/Sponsor
Name: Cephalon, Inc.
Address: 41 Moores Road, P.O. Box 4011, Frazer, PA 19355
Representative: Sherry Carenzo
Telephone: 610-727-3411

Name of Reviewer: Erika Pfeiler, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: PAS

2. SUBMISSION PROVIDES FOR: Change in presentation from a lyophilized powder to a sterile non-aqueous solution

3. MANUFACTURING SITE: Baxter Oncology GmbH
Kantstrasse 2
Halle, Germany 33790

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
Sterile, non-aqueous solution for intravenous infusion
45 mg/vial or 180 mg/vial (90 mg/ml)
2R amber glass vial with 13 mm rubber stopper

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

6. PHARMACOLOGICAL CATEGORY: Treatment of chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphoma

B. SUPPORTING/RELATED DOCUMENTS:
Microbiology Review 24 of DMF (b) (4) (DARRTS Date 26 April 2013)
Product Quality Microbiology Memorandum (DARRTS Date 26 April 2011)

C. REMARKS:
This supplement proposes the introduction of a liquid form of the drug product in a single dose vial to replace the currently approved lyophilized form. Two volumes of drug product are proposed, 0.5 ml and 2 ml. This supplement was submitted in the eCTD format.

filename: N2249S015R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4) (b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

Erika Pfeiler, Ph.D.
Microbiologist

B. Endorsement Block_____

John Metcalfe, Ph.D.
Senior Review Microbiologist

C. CC Block
N/A

Following this page, 10 pages withheld in full - (b)(4)

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/s/

ERIKA A PFEILER
06/06/2013

JOHN W METCALFE
06/06/2013
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	22-249/S-015	**Reviewer:** Houda Mahayni, Ph.D.	
Submission Dates:	March 8, 2013 May 10, 2013		
Division:	DHP	**Acting Team Leader:** Sandra Suarez, Ph.D.	
Applicant:	Cephalon Inc.	**Acting Supervisor:** Richard Lostritto, Ph.D.	
		Secondary Reviewer: Acting Team Leader	
Trade Name:	(b) (4)	**Date Assigned:**	April 11, 2013
Generic Name:	Bendamustine Hydrochloride (b) (4) Injection	**PDUFA Date:**	July 8, 2013
		Date of Review:	June 13, 2013
Indication:	Treatment of patients with chronic lymphocytic leukemia	**Type of Submission:** Prior Approval Supplement	
Formulation/strengths	Sterile solution/ 45 mg/vial and 180/vial		
Route of Administration	Intravenous (IV)		
Biopharmaceutics Review Focus: Biowaiver Request			

SUBMISSION:

FDA approved Treanda® (bendamustine hydrochloride) for Injection (NDA 22-249) on March 20, 2008. The purpose of this Prior Approval Supplement is to replace the existing lyophilized formulation of Treanda® containing either 25 mg/vial or 100 mg/vial of bendamustine hydrochloride with a sterile solution formulation containing either 45 mg/vial or 180 mg/vial of bendamustine hydrochloride.

The Applicant stated that the purpose of developing the formulation stems from the need to overcome dilution errors reported due to incorrect reconstitution with saline and to improve product administration.

This Biopharmaceutics review focuses on the evaluation of the acceptability of the biowaiver request for the proposed formulation.

BIOPHARMACEUTIC INFORMATION:

The Applicant requested a biowaiver for the in vivo bioequivalence and bioavailability studies. The Applicant stated that the information provided supports the biowaiver request and addresses 21 CFR 320.22(b)(1) requirements, specifically:

- the proposed liquid formulation for injection contains the same active ingredient as the currently approved Treanda® drug product;
- both products are diluted into infusion bags to produce the same concentration prior to intravenous infusion;
- the two inactive ingredients in the new formulation, N,N-dimethylacetamide (DMA) and propylene glycol, are listed in the FDA's Inactive Ingredient (IIG) Database;

- the inactive ingredients have previously been approved for use in a product with the same route of administration, at levels significantly above those contained in the proposed liquid solution formulation of Treanda®.

On May 1, 2013, FDA requested of the Applicant the following information:

As per 21 CFR § 320.22 (b), FDA shall waive the requirement for submission of demonstrating bioequivalence if the drug product is a parenteral solution for injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. In addition, your product should have similar pH, tonicity and osmolarity to the approved product. Therefore, FDA shall not grant biowaiver for demonstration of bioequivalence unless your proposed product has similar concentration, pH, tonicity and osmolarity to the approved product unless you submit justification on the lack of clinical relevance of the proposed variations on these parameters including the absence of mannitol. Therefore, please provide information/justification supporting that the in vivo physiological disposition of Bendamustine hydrochloride from your proposed product formulated without mannitol will not be different than that of the approved product.

The Applicant responded on May 10, 2013 providing justifications in response to the requested information of May 1, 2013. The data provided showed that the active concentration, pH, and osmolality in both current and proposed formulations are similar.

In regards to mannitol, the Applicant stated that in the currently approved lyophilized drug, mannitol is [redacted] (b) (4)

According to the Applicant, mannitol does not affect the bioavailability of bendamustine, and therefore differences in the presence or absence of mannitol are not expected. In support of this assertion, the Applicant submitted a pharmacokinetics study in monkeys to show that the in vivo physiological disposition of bendamustine hydrochloride from the proposed product formulated without mannitol is not different than that of the approved product. However, the acceptability of this pharmacokinetics study in monkeys (Studies DP-2008-107 and DS-2012-013), will be determined by the PharmTox review team.

CONCLUSIONS:

Although the excipients in the current and proposed formulations are not the same, the excipients amount is negligible (each < 0.4% in a 500 mL infusion) (refer to PharmTox review for the qualification of these excipients). The amount of mannitol per treatment for a patient of 1.8 m^2 is 1224 mg which is equivalent to a total of 1.224 g mannitol per treatment over 60 minutes on days 1 and 2. This amount of mannitol (1.224 g) is less than the amount of mannitol used to induce diuresis (20 g of mannitol given IV over 5 minutes). Bendamustine is primarily metabolized to 2 active minor metabolites, M3 and M4. The 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 caused by bendamustine. In addition, any increase in urine flow

would not be expected to decrease systemic exposure to bendamustine since it is mainly eliminated by metabolism and the metabolites are mainly eliminated through feces. Therefore, the amount of mannitol included in the proposed formulation is not expected to alter the disposition of the drug product and its metabolites.

RECOMMENDATION
From the perspective of Biopharmaceutics, NDA 22-249 (S015) is recommended for APPROVAL.

A Biowaiver can be granted for the proposed formulation provided that the preclinical pharmacokinetic studies (Study DP-2008-107 and Study DS-2012-013) and the amount of DMA (dimethylacetamide) in the proposed formulation are found acceptable by the PharmTox review team.

APPROVAL SIGNATURES: {see electronic signature page}

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: *NDA 22-249/S-015 DARRTS, RLostritto*

BIOPHARMACEUTICS EVALUATION - REVIEW NOTES

1.0 GENERAL INFORMATION

1.1 Relevant Regulatory History

NDA 22-249 for Treanda® (bendamustine hydrochloride) for Injection was approved on March 20, 2008. The 25 mg vial was approved under Supplement S001 on May 1, 2009.

1.2 Drug Substance Summary

The Applicant stated that bendamustine hydrochloride is (b) (4) (b) (4) used in the manufacture of the drug product. Therefore, the physical characteristics of the drug substance are not considered to significantly influence the performance of the drug product.

1.3 Drug Product Summary

Treanda® is currently approved as a single-use vial containing either 25 mg/vial or 100 mg/vial of bendamustine hydrochloride as a lyophilized powder that is reconstituted with Sterile Water for Injection, USP. The appropriate volume is withdrawn and transferred into a 500 mL infusion bag of either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextroxe/0.45% Sodium Chloride Injection, USP for administration by infusion based on body surface area.

The proposed formulation is a single-use vial containing either 45 mg/vial or 180 mg/vial of bendamustine hydrochloride as a sterile solution formulation. The proposed formulation is a 90 mg/mL solution (b) (4) N, N dimethylacetamide (DMA) and (b) (4) propylene glycol. The Applicant stated that the proposed formulation will be placed in a 500 mL infusion bag of either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection to produce the same concentration as the approved formulation prior to intravenous infusion. The Applicant claims that differences in bioavailability are not expected in humans based on demonstrated lack of difference in pharmacokinetics between the two formulations in monkeys.

The composition of bendamustine solution, 45 mg/vial and 180 mg/vial, and the function of each ingredient are listed in Table 1.

Table 1: Composition of the Drug Product

Component	Reference to standard	Function	Amount per vial (45 mg strength)	Amount per vial (180 mg strength)
Bendamustine HCl	In house standard	Active ingredient	45 mg	180 mg
Propylene glycol	USP	(b) (4)	162 mg	648 mg
N,N-Dimethylacetamide	EP		293 mg	1172 mg

2.0 BIOPHARMACEUTICS REVIEW TOPICS

2.1 BIOWAIVER REQUEST

A comparison of the approved lyophilized powder and the proposed liquid solution formulations is presented in Table 2.

Table 2: Comparison of Lyophilized Powder (approved) and Liquid Solution (proposed) Dosage Forms

Attribute	Lyophilized Powder for Reconstitution (Current Formulation)	Liquid Solution (New Formulation)
Composition of drug product	Bendamustine hydrochloride, mannitol (b) (4)	Bendamustine hydrochloride, propylene glycol, N,N-dimethylacetamide
Dosage strength per vial	25 mg/vial and 100 mg/vial	45 mg/vial and 180 mg/vial
Preparation for dilution into the infusion bag	Reconstitute with Sterile Water for Injection (SWFI), USP (5 mL for the 25 mg/vial or 20 mL for the 100mg/vial)	No reconstitution is required. The solution concentration in the vial is 90 mg of bendamustine HCl per mL (0.5 mL of the 45 mg/vial or 2 mL of the 180 mg/vial).
Recommended diluents	0.9% Sodium Chloride Injection, USP (normal saline) or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP	0.9% Sodium Chloride Injection, USP (normal saline) or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP
Final Concentration in the infusion bag for a 100 mg/m^2 dose and a 1.80 m^2 patient	0.3 mg/mL	0.3 mg/mL

The excipients in the drug product solution are different from the excipients in the currently approved lyophilized drug product formulation. The currently approved lyophilized drug product is manufactured using mannitol (b) (4) (b) (4). The proposed liquid solution drug product formulation is manufactured using (b) (4) N, N-dimethylacetamide and (b) (4) propylene glycol.

The Applicant stated that the amount of N, N-demethlyacetamide and propylene glycol is negligible and the active ingredient delivered to the patient by IV infusion in both formulations can be considered equivalent. A comparison of the amount of excipients delivered by IV infusion (<0.4% in a 500 mL of diluent) is shown in Table 3.

Table 3: Excipient Comparison Between the Current Formulation and Proposed Liquid Solution Formulation (Submission dated 3/8/13)

Attribute	Current Formulation	Proposed Liquid Solution Formulation	
Excipient	Mannitol	N,N-dimethlyacetamide (DMA)	Propylene glycol (PG)
Dose[1]	100 mg/m^2 -120 mg/m^2 day 1 and day 2	100 mg/m^2 -120 mg/m^2 day 1 and day 2	
Amount of excipient per dose for a patient of 1.8 m^2	170 mg - 612 mg of mannitol	1172 – 1406 mg of DMA (1.3 - 1.6 mL)	648 – 778 mg of PG (0.68 – 0.82 mL)
Total amount of excipient per treatment	340 mg – 1224 mg of mannitol	2344 – 2812 mg of DMA (2.6 - 3.2 mL)	1296 – 1556 mg of PG (1.36 – 1.64 mL)
Excipient in 500 mL infusion (%)	0.07% - 0.24%	0.26% - 0.32%	0.14 % - 0.16 %

[1] The calculated dose range is based on 1.8 m^2 for doses of 100 mg/m^2 and 120 mg/m^2

FDA sent an Information Request on May 1, 2013 requesting the following:
As per 21 CFR § 320.22 (b), FDA shall waive the requirement for submission of demonstrating bioequivalence if the drug product is a parenteral solution for injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. In addition, your product should have similar pH, tonicity and osmolarity to the approved product. Therefore, FDA shall not grant biowaiver for demonstration of bioequivalence unless your proposed product has similar concentration, pH, tonicity and osmolarity to the approved product unless you submit justification on the lack of clinical relevance of the proposed variations on these parameters including the absence of mannitol. Therefore, please provide information/justification supporting that the in vivo physiological disposition of Bendamustine hydrochloride from your proposed product formulated without mannitol will not be different than that of the approved product.

The Applicant responded on May 10, 2013, stating that the biowaiver request is supported by the following:
• *The new liquid formulation contains the same active ingredient as the currently approved Treanda® drug product, and once diluted into a 500 mL infusion bag is at the same concentration; also the pH and osmolality are similar*
• *Since the solution in the IV bag is > 99% diluent, the amount of inactive ingredients in either formulation is not considered to affect the bioavailability of the drug. The bendamustine HCl solution is delivered to the patient by IV infusion in both formulations and can be considered equivalent*

• *No differences in bioavailability are expected in humans based on the demonstrated lack of difference in pharmacokinetic profile between the two formulations in monkeys*

Also, the Applicant submitted a comparison of pH and osmolality of formulations in the recommended diluents, as presented in Table 4.

Table 4: Comparison of the Current Lyophilized Powder and New Liquid Formulations in 500 mL IV Bags

Attribute	Lyophilized Powder (Current Formulation)	Liquid (New Formulation)
Preparation for dilution into the infusion bag	Reconstitute with Sterile Water for Injection (SWFI), USP Transfer the appropriate dose to a 500 mL infusion bag for IV administration	**No reconstitution necessary** Transfer the appropriate dose to a 500 mL infusion bag for IV administration
Recommended diluents	0.9% Sodium Chloride Injection, USP (normal saline) or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP	0.9% Sodium Chloride Injection, USP (normal saline) or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP
Final Concentration in the infusion bag for a 100 mg/m^2 dose and a 1.80 m^2 patient	0.3 mg/mL	0.3 mg/mL
pH[1]		
0.9% Sodium Chloride Injection, USP	3.79	3.81
2.5% Dextrose/0.45% Sodium Chloride Injection, USP	3.72	3.76
Osmolarity[1] (mOsmols/kg)		
0.9% Sodium Chloride Injection, USP	271	326
2.5% Dextrose/0.45% Sodium Chloride Injection, USP	263	319

[1] Concentration in the infusion bag for a 100 mg/m^2 dose and a 1.80 m^2 patient

The Applicant concluded that the pH of all admixture solutions is similar and the osmolality of the solutions ranged from 263-326 mOsmols/kg are considered similar and have acceptable tonicity for IV infusion (See Table 4).

Reviewer's Assessment: ***Satisfactory***.
The Applicant provided Table 4 to show that pH and osmolality is equivalent in both the current and proposed formulations. This reviewer verified the acceptable range of osmolality in human blood and found that serum osmolality range between 282-295 mOsm/kg water (reference: http://infusionnurse.org/2010/05/14/osmolarity-vs-osmolality/), and plasma osmolarity is 290 mOsm/L with a range of 285-310 mOsm/L (reference: Stranz M. A review of pH and osmolarity. International Journal of Pharmaceutical Compounding 2002; Vol. 6, No. 3, May/June: 216-220). It is noted that the Applicant reported the osmolality range of 263-326 mOsmols/kg for both

formulations which is slightly higher in the proposed formulation and slightly higher than serum osmolality range of 282-295 mOsm/kg). However, both osmolality values in the current and proposed formulations can be considered similar and are not significantly different than the normal osmolality of extracellular fluid range of 282-295 mOsm/kg.

Furthermore, the Applicant stated that in the currently approved lyophilized drug, mannitol is (b) (4) . According to the Applicant, mannitol does not affect the bioavailability of bendamustine, and therefore differences in the presence or absence of mannitol are not expected. (b) (4)

According to the Product Label of Bendamustine (See references: Facts & Comparisons® eAnswers on Mannitol), in vitro data indicate that bendamustine is primarily metabolized via hydrolysis to 2 active minor metabolites with low cytotoxic activity (M3 and M4). These metabolites 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 caused by bendamustine. No mass balance study has been undertaken in humans. Preclinical radiolabeled bendamustine studies showed that approximately 90% of the administered drug was recovered in excreta, primarily in the feces. Bendamustine clearance in humans is approximately 700 mL/min. After a single IV dose of bendamustine 120 mg/m^2 over 1 hour, the intermediate half-life of the parent compound is approximately 40 minutes. The mean apparent terminal elimination half-lives 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.

It is noted that the Applicant reported different amounts of mannitol per treatment in the provided tables (Table 3 provided in Submission dated 3/8/13 and Table 5 provided in Submission dated 5/10/13). However, if the higher amount of mannitol (1224 mg) per treatment for a patient of 1.8 m^2 is taken as the amount administered, then the reported amount in Table 3 of 1224 mg is equivalent to a total of 1.224 g mannitol per treatment over 60 minutes on days 1 an 2 which is less than the amount of mannitol used to induce diuresis (20 g of mannitol given IV over 5 minutes). (See references http://home.intekom.com/pharm/intramed/manitl20.html, and http://www.mims.com/USA/drug/info/Mannitol%20Injection%20Solution/?type=full).

Bendamustine is primarily metabolized to 2 active minor metabolites, M3 and M4. The 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 caused by bendamustine. Any increase in urine flow would not decrease systemic

exposure to bendamustine. Furthermore, the amount of mannitol included in the proposed formulation is not hypermolar and therefore would not induce diuresis.

The Applicant provided a comparison of the amount of excipients delivered by IV infusion (in 500 mL of diluent) in Table 5. The Applicant indicated that the amounts of mannitol, N,N-dimethylacetamide and propylene glycol are negligible (each < 0.4% in a 500 mL infusion) and solution of bendamustine HCl delivered to the patient by IV infusion in both formulations can be considered equivalent.

Table 5: Excipient Comparison of the Current Formulation and the New Solution Formulation (Submission dated 5/10/13)

Attribute	Current formulation	New solution formulation	
Excipient /Function	Mannitol (b) (4)	N,N-dimethlyacetamide (DMA) (b) (4)	Propylene glycol (PG) (b) (4)
Dose[1]	100 mg/m^2 -120 mg/m^2 day 1 and day 2	100 mg/m^2 -120 mg/m^2 day 1 and day 2	
Amount of excipient per dose for a patient of 1.8 m^2	306 mg - 367 mg of mannitol	1226 – 1509 mg of DMA (1.3 - 1.6 mL)	727 – 830 mg of PG (0.7 – 0.8 mL)
Total amount of excipient per cycle	612 mg – 734 mg of mannitol	2452 – 3018 mg of DMA (2.6 - 3.2 mL)	1453 – 1661 mg of PG (1.4 – 1.6 mL)
Excipient in 500 mL infusion (%)	0.06% - 0.07%	0.26% - 0.32%	0.14% - 0.16%

[1] The calculated dose range is based on 1.8 m^2 for doses of 100 mg/m^2 and 120 mg/m^2

Reviewer's Note:
The Applicant reported different amount of excipient per dose for a patient of 1.8 m^2, different total amount of excipient per treatment, and different excipient in 500 mL infusion (%) between the current and proposed liquid formulation in both tables (Table 3 and Table 5) above.

The Applicant referred again to the pharmacokinetic study in monkeys which showed that the pharmacokinetic profiles of bendamustine, metabolites (M3, and M4) for the liquid formulation of bendamustine HCl were qualitatively and quantitatively similar to those obtained for the Treanda® formulation after single bolus intravenous doses to monkeys (see Table 6, Figure 1, and Figure 2 below). A short description of the pharmacokinetics study in monkeys and other studies submitted in support of the biowaiver request are summarized below.

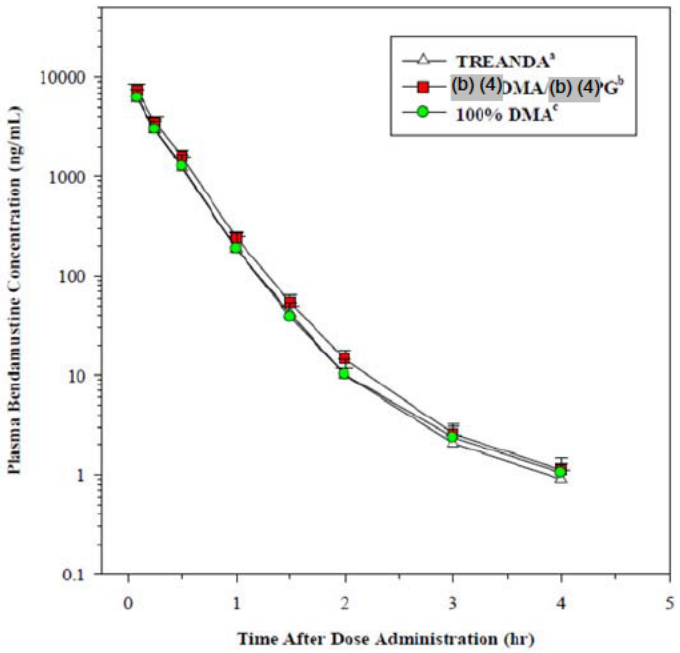
Summary of the PharmTox Studies submitted in support of the Biowaiver Request.
The Applicant conducted a pharmacokinetic study (Study DP-2008-107) in cynomolgus monkeys to compare the pharmacokinetic profile of single bolus intravenous doses of bendamustine HCl prepared from the currently marketed lyophilized powder formulation (Treanda®) and the liquid formulation in (b) (4) N, N-dimethylacetamide (DMA) and (b) (4) propylene glycol (PG). In this study, the Applicant compared three formulations: Treanda® for Injection, (b) (4) N,N-dimethylacetamide/ (b) (4) propylene glycol, and 100% N, N dimethylacetamide.

Each formulation was diluted with 0.9% Saline, USP prior to infusion. The mean pharmacokinetic parameter estimates for bendamustine from the 3 formulations tested are presented in Table 6, and the corresponding mean plasma concentration-versus-time profiles for bendamustine and its metabolites are shown in Figure 1 and Figure 2. The Applicant stated that the shapes of the mean plasma concentration-versus-time profiles of bendamustine were similar between each of the 3 formulations. Therefore, the Applicant concluded that differences in bioavailability are not expected in humans.

Table 6: Mean Pharmacokinetic Parameter Estimates after Intravenous Administration of Bendamustine Formulations to Male Cynomolgus Monkeys

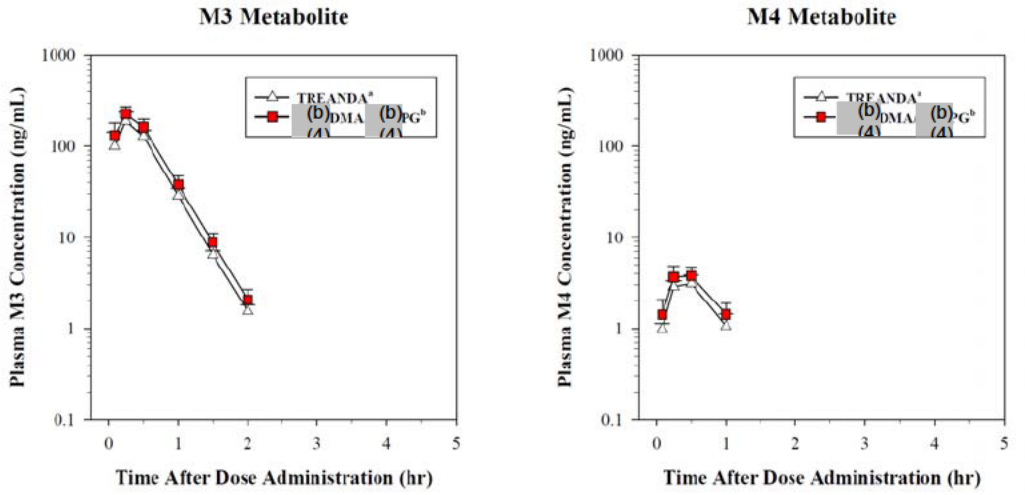
Formulation	Conc. (mg/mL)	C_{max} (ng/mL)	T_{max} (hours)	$T_{½}$ (hours)	$AUC_{0-\infty}$ (ng*hr/mL)
Treanda® for Injection	5	6037 ± 2456	0.083	0.57	2314 ± 800
100% N,N-dimethylacetamide	45	6209 ± 1300	0.083	0.63	2372 ± 535
(b) (4) N,N-dimethylacetamide /(b) (4) propylene glycol	90	7380 ± 1170	0.083	0.54	2854 ± 398

Figure 1: Mean + SD Plasma Concentration-Versus-Time Profiles of Bendamustine in Male Cynomolgus Monkeys (N=4) Administered Single 3-mg/kg Bolus Intravenous Doses of Bendamustine in 3 Different Formulations



a The dose formulation was prepared by reconstituting 25-mg vials of TREANDA with 8.3 mL of 0.9% NaCl.
b The dose formulation was prepared by diluting 1 mL of 90-mg/mL stock solution of CEP-18083 in (b) (4) N,N-dimethylacetamide (b) (4)PG with 30 mL of 0.9% NaCl.
c The dose formulation was prepared by diluting 1 mL of 45-mg/mL stock solution of CEP-18083 in 100% N,N-dimethylacetamide with 15 mL of 0.9% NaCl.

Figure 2: Mean + SD Plasma Concentration-Versus-Time Profiles of M3 and M4 Metabolites in Monkeys Administered a Single Bolus Intravenous Dose of Treanda or New Bendamustine Solution



a The dose formulation was prepared by constituting 25-mg vials of TREANDA with 0.9% NaCl.
b The dose formulation was prepared by diluting a 90-mg/mL stock solution of bendamustine in (b) (4) DMA/(b) (4) PG with 0.9% NaCl.

Additionally, the Applicant tested the new formulation in a 15 week intermittent intravenous infusion toxicity study in rats (Study DS-2012-013). The dosing solution had varying concentration of 2 propylene glycol esters ((b) (4) and (b) (4); 4:1 ratio). The toxicity of the highest dose evaluated is 15 mg/kg/dose bendamustine+1.5 mg/kg/dose propylene glycol esters and compared to a bendamustine solution alone at a dose of 15 mg/kg/dose. The Applicant reported that the toxicological profile of the highest dose of bendamustine solution with and without propylene glycol esters was comparable.

Furthermore, the Applicant reviewed the safety profile of Busulfex® (DSM Pharmaceuticals, Inc), an approved product that contains (b) (4) of DMA. The Applicant reported that the daily recommended dose of this marketed formulation contains a DMA equivalent of 42% of the maximum tolerated dose of 14.8 g/m^2/day. However, the DMA in the proposed formulation of Treanda®, a dose of 120 mg/m^2 of bendamustine HCl would expose the patient to 0.781 g/m^2/day of DMA. The Applicant concluded that the reduced volume of this excipient is not expected to have an adverse safety profile.

Reviewer's Assessment: The acceptability of the above studies will be determined by the PharmTox reviewer. It is noted that bendamustine is

metabolized to two active metabolites M3 and M4. Therefore, the acceptability of the study in monkeys becomes questionable unless there is evidence that there are no differences in metabolism between monkeys and humans for this drug. However, since the metabolites concentration in plasma is so small compared to bendamustine ($^1/_{10}$ and $^1/_{100}$ that of the parent compound, respectively), suggesting that the cytotoxic activity is primarily caused by bendamustine, it may be feasible to relay on pharmacokinetics study in monkeys data. Nevertheless, the mannitol amount in the proposed formulation is not considered significant enough to increase urine flow and cause decrease in the systemic exposure of bendamustine. Furthermore, the amounts of mannitol included in the proposed formulation is not hypermolar and therefore would not be expected induce diuresis.

Overall Reviewer's Evaluation: ***Satisfactory***

For both formulations, current and proposed, the active is the same and the final concentration of bendamustine in the infusion bag based on 100 mg/m^2 dose for a 1.8 m^2 patient (Table 4) is the same concentration (0.3 mg/mL). Although the inactive ingredients are not the same, the Applicant provided the following justifications:

- Submitted a pharmacokinetics study in monkeys to show that the plasma-concentration versus time profiles is similar for the drug and its metabolites for the two formulations as a justification for the lack of clinical relevance of mannitol effect on the in vivo physiological disposition of Bendamustine hydrochloride (The acceptability of this study to be determined by the PharmTox reviewer).
- Provided Table 4 to show that the active concentration in both current and proposed formulation is similar.
- Provided Table 4 to show that pH and osmolality is equivalent in both the current and proposed formulations. This reviewer verified the acceptable range of osmolality in human blood and found that serum osmolality range between 282-295 mOsm/kg water (reference: http://infusionnurse.org/2010/05/14/osmolarity-vs-osmolality/), and plasma osmolarity is 290 mOsm/L with a range of 285-310 mOsm/L (reference: Stranz M. A review of pH and osmolarity. International Journal of Pharmaceutical Compounding 2002; Vol. 6, No. 3, May/June: 216-220). It is noted that the Applicant reported the osmolality range of 263-326 mOsmols/kg of both formulations which is slightly higher in the proposed formulation and slightly higher than serum osmolality range of 282-295 mOsm/kg). Both of the osmolality values in the current and proposed formulations can be considered similar and are not significantly different than the normal osmolality of extracellular fluid range of 282-295 mOsm/kg.
- Provided Table 5 to show that although the excipients are different, the excipients amounts of mannitol, N, N-dimethylacetamide and propylene glycol are negligible (each < 0.4% in a 500 mL infusion). Therefore, the solution of bendamustine HCl delivered to the patient by IV infusion in both formulations can be considered equivalent. Also, the amount of mannitol per treatment for a patient of 1.8 m^2 is 1224 mg which is equivalent to a total of 1.224 g mannitol per treatment over 60 minutes on days 1 and 2. This amount

of mannitol (1.224 g) is less than the amount of mannitol used to induce diuresis (20 g of mannitol given IV over 5 minutes). Hence, mannitol is not expected to have an effect on bendamustine disposition given that it is metabolized to M3 and M4 and these metabolites in plasma are $^1/_{10}$ and $^1/_{100}$ that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily caused by bendamustine. Furthermore, the amount of mannitol included in the proposed formulation is not hypermolar and therefore would not induce diuresis. Therefore, the biowaiver request can be granted from the Biopharmaceutics perspective provided the PharmTox studies are found acceptable.

Reviewer's Conclusion: *A waiver of bioequivalence studies to qualify the proposed liquid solution formulation can be granted, if the PharmTox studies (Study DP-2008-107 and Study DS-2012-013), and the amount of DMA in the proposed formulation are found acceptable by the PharmTox reviewer.* Although the excipients in the current and proposed formulations are not the same, the excipients amount is negligible (each < 0.4% in a 500 mL infusion). Also, the amount of mannitol per treatment for a patient of 1.8 m^2 is 1224 mg which is equivalent to a total of 1.224 g mannitol per treatment over 60 minutes on days 1 and 2. This amount of mannitol (1.224 g) is less than the amount of mannitol used to induce diuresis (20 g of mannitol given IV over 5 minutes). Therefore, mannitol is not expected to have an effect on bendamustine disposition given that it is metabolized to M3 and M4 and these metabolites in plasma are $^1/_{10}$ and $^1/_{100}$ that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily caused by bendamustine. If the Applicant's claim of the lack of clinical relevance of mannitol effect on the in vivo physiological disposition of Bendamustine hydrochloride is found acceptable by the PharmTox reviewer based on the pharmacokinetics study in monkeys, then the Biowaiver request can be granted because of an acceptable justification.

3.0 CONCLUSIONS AND RECOMMENDATIONS

The Prior Approval Supplement (S015) is recommended for APPROVAL, from the perspective of Biopharmaceutics.

A Biowaiver can be granted for the proposed liquid solution formulation provided that the PharmTox studies (Study DP-2008-107 and Study DS-2012-013), and the amount of DMA in the proposed formulation are found acceptable by the PharmTox reviewer.

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/s/

HOUDA MAHAYNI
06/26/2013

SANDRA SUAREZ
06/26/2013

Memorandum

NDA	22249/SDN #316
Submission Date:	08 March 2013
Brand Name:	Treanda®
Generic Name:	Bendamustine hydrochloride
Formulation:	(b) (4) Injection
OCP Reviewers:	Rachelle M. Lubin, Pharm.D.
OCP Team Leader:	Julie Bullock, Pharm.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Hematology Products
Sponsor:	Cephalon
Submission Type:	Prior Approval Supplement (S-015)
Dosage Form & Strength:	Sterile Solution; 45 mg/vial and 180 mg/vial
Indications	Treatment of patients with chronic lymphocytic leukemia

Treanda® (bendamustine hydrochloride) was approved for injection on March 20, 2008 (NDA 22249) for the treatment of chronic lymphocytic leukemia (CLL). The purpose of this prior approval CMC supplement NDA (S-015) is to replace the existing lyophilized formulation of Treanda® with a sterile solution injectable formulation.

The original NDA was reviewed by Dr. Julie Bullock on February 19, 2008. On December 1, 2010 (SDN 96) the sponsor submitted their mass balance study (Study Report 1039) to fulfill a post-marketing commitment (PMC #2) issued under the original NDA, which was reviewed Dr. Young Jin Moon (date 12/01/2011). In the current supplement NDA (S-015, SDN 316) the sponsor made reference to concentration levels of metabolite HP1 (inactive), but no analytical method report for HP1 measurement was provided in during the PMC mass balance study submission. Therefore, the sponsor has provided the bioanalytical method report (Study Report DP-2010-014) for HP1 to the current CMC supplement NDA submission. As a result, CMC has requested that Clinical Pharmacology/Division 5 review the submitted study report and more specifically verify whether metabolite HPL1 (CEP-43714) is 10% of bendamustine concentration levels.

During method development, HP1 was highly unstable in both plasma and urine. The applicant could not reliably quantify HP1 metabolite concentrations in plasma. Therefore no validated bioanalytical method for quantitative analysis of HP1 was performed in the mass balance study (study 1039). Instead a semi-quantitative assessment of HP1 in plasma (and urine) was performed to provide systemic exposure of HP1. MS/MS transitions were monitored for HP1 (m/z 340.2 – 322.0) during the HPLC/MS/MS analysis of HP2 (Study Report DP-2010-014). HP1 concentrations were estimated based on a validated HPLC-MS/MS assay for HP2 measurement, which this method was found acceptable by Clinical Pharmacology/Division 5 in December 2011 (SDN 96). In regards to a method for HP1, the applicant was unable to stabilize HP1to allow sample processing and facilitate storage.

Study DP-2010-014 was a semi-quantitative determination of HP1 in human plasma and urine. MS/MS transitions were monitored for HP1 (m/z 340.2 – 322.0) during the validated HPLC/MS/MS analysis of HP2 (refer to the PMC review of Study Report DP-2010-014, dated 12/01/2011). Stock solutions of both metabolites were prepared in methanol at a target concentration of 1 mg/mL, which were then diluted and spiked into plasma to provide target concentrations of 500 ng/mL of HP1 and HP2 in plasma. The response ratio (HP1:HP2) was determined to be 1.84 in plasma. To establish analytical method precision for HP1, the area of HP1 in calibration samples spiked with HP2 were determined. HP1 peak areas were determined in the samples collected from Study 1039. To correct for variation, the HP1 peak areas were divided by the area of the internal standard (b) (4). The relative standard deviation of the peak ratios (area HP1/area HP2) was 9.8% (n=53). Corrected area ratios for HP1 were used to calculate the concentrations of HP1 using the calibration curve parameters of HP2. These values are rough estimates of the actual concentration values.

A total of 6 analytical runs were performed for the analysis of HP2. HP1 concentrations were estimated in plasma and urine samples that were analyzed for HP2. Plasma samples from 6 patients were utilized. Results show that the estimated mean Cmax values for HP1 was 620.6 ng/mL. Based on these findings, compared to bendamustine (parent) concentration levels, metabolite HP1 is 11.7% of parent mean Cmax (5319.1 ng/mL). However, this level should be interpreted with caution because the method to quantify HP1 in plasma was not validated.

RECOMMENDATION

The Office of Clinical Pharmacology/Division 5 reviewed Study DP-2010-014 from a clinical pharmacology perspective. We defer to CMC regarding the overall acceptability of supplement NDA 22249 (S-015) and the acceptability of the level of HP1 measured using an unvalidated bioanalytical method.

Action

No further action.

Reviewer: Rachelle M. Lubin, Pharm.D.
Division of Clinical Pharmacology 5

Team Leader: Julie Bullock, Pharm.D.
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **T Carioti;** MTL - **A George**; MO - **V Kwitkowski**
DCP-5: Reviewer - **R Lubin**, TL - **J Bullock,** DDD - **B Booth**,
DD - **A Rahman;**

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/s/

RACHELLE M LUBIN
07/01/2013

JULIE M BULLOCK
07/01/2013

BIOPHARMACEUTICS REVIEW -- ADDENDUM

Office of New Drug Quality Assessment

Application No.:	NDA 22-249/S-015	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DHP		
Applicant:	Cephalon Inc.	**Acting Team Leader:** Sandra Suarez, Ph.D.	
Trade Name:	Treanda®	**Acting Supervisor:** Richard T. Lostritto, Ph.D.	
Generic Name:	Bendamustine Hydrochloride	**Date Assigned:**	April 11, 2013
Indication:	Treatment of patients with chronic lymphocytic leukemia	**Date of Review:**	July 1, 2013
Formulation/strength	Sterile solution/ 45 mg/vial and 180/vial		
Route of Administration	Intravenous (IV)		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates:	**Dates of Consult**	**PDUFA DATE**
March 8, 2013 May 10, 2013	April 11, 2013	July 8, 2013

Reason for review addendum:	To reflect the PharmTox findings and its impact on the acceptability of the biowaiver request
Key review points	Biowaiver Request

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

FDA approved Treanda® (bendamustine hydrochloride) for Injection (NDA 22-249) on March 20, 2008. The purpose of this Prior Approval Supplement is to replace the existing lyophilized formulation of Treanda® containing either 25 mg/vial or 100 mg/vial of bendamustine hydrochloride with a sterile solution formulation containing either 45 mg/vial or 180 mg/vial of bendamustine hydrochloride in (b) (4) N, N dimethylacetamide (DMA) and (b) (4) propylene glycol (PG).

The following documents are referred to in this review:

- The Biopharmaceutics review in DARRTS of this supplement and by this reviewer (see Houda Mahayni's review dated June 26, 2013).
- Memorandum by Dr. Haleh Saber dated June 28, 2013.
- Pharmacology/Toxicology NDA review by Dr. Ramadevi Gudi dated June 17, 2013.

This review focuses on the evaluation of the acceptability of the biowaiver request for the proposed formulation.

The Acceptability of the Biowaiver Request

In the Biopharmaceutics review dated June 26, 2013, the biowaiver request was found acceptable provided that the preclinical pharmacokinetics studies and the amount of DMA (dimethylacetamide) in the proposed formulation are found acceptable by the PharmTox review team. Based on Pharm Tox findings that the pharmacokinetic profiles of bendamustine and its two metabolites (M3 and M4) were similar in the 3 different Treanda formulations: approved Treanda® formulation, the to-be-marketed bendamustine formulation, and 100% DMA formulation (See Pharm Tox Review dated June 17, 2013), and that there are no safety issues related to the amount of DMA in Treanda (See Pharm Tox Memo date June 28, 2013), the biowaiver request can be granted for the proposed formulation.

II) RECOMMENDATION

From the Biopharmaceutics perspective, NDA 22-249 (S015) for Treanda (Bendamustine Hydrochloride) Sterile Solution is recommended for APPROVAL.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

HOUDA MAHAYNI
07/02/2013

SANDRA SUAREZ
07/02/2013

BIOPHARMACEUTICS REVIEW -- ADDENDUM Office of New Drug Quality Assessment		
Application No.:	NDA 22-249/S-015	**Reviewer:** Houda Mahayni, Ph.D.
Division:	DHP	
Applicant:	Cephalon Inc.	**Acting Team Leader:** Sandra Suarez, Ph.D.
Trade Name:	Treanda®	**Acting Supervisor:** Richard T. Lostritto, Ph.D.
Generic Name:	Bendamustine Hydrochloride	**Submission Date:** July 26, 2013
Indication:	Treatment of patients with chronic lymphocytic leukemia	
Formulation/strength	Sterile solution/ 45 mg/vial and 180/vial	**PDUFA Date:** November 26, 2013
Route of Administration	Intravenous (IV)	Addendum to Biopharmaceutics Review

As stated in the Biopharmaceutics review dated June 26, 2013 for Treanda (bendamustine hydrochloride) for Injection, a biowaiver under 21 CFR 320.22(b) was granted for this application as per the Applicant's request. As discussed in the review, although the proposed formulation included different excipients, based on the provided information we determined that the differences in these excipients are unlikely to alter the systemic exposure of the product. This addendum to the original review is intended to clarify that although the biowaiver 21 CFR 320.22(b) requirements were not fully met, the Applicant provided adequate information that let us conclude that as a scientific matter bioequivalence has been demonstrated given the overall supportive scientific evidence. This scientific conclusion is consistent with 21 CFR Part 320.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

HOUDA MAHAYNI
09/09/2013

SANDRA SUAREZ
09/09/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 27, 2013
Reviewer:	Kevin Wright, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Treanda (b) (4) Injection 45 mg per 0.5 mL and 180 mg per 2 mL (90 mg per mL)
Application Type/Number:	NDA 022249
Submission Number:	S-015
Applicant/sponsor:	Teva Pharmaceutical USA, Inc.
OSE RCM #:	2013-694

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Contents

1 Introduction 1
1.1 Regulatory History 1
1.2 Product Information 1
2 Methods and Materials Reviewed 2
2.1 Selection of Medication Error Cases 2
2.2 Labels and labeling 2
3 Medication Error Risk Assessment 3
3.1 Medication Error Cases 3
3.2 Integrated Summary of Medication error risk assesment 4
4 Conclusions 4
5 Recommendations 5
Appendices 7
Appendix A. Database Descriptions 7

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for (b) (4) under NDA 022249 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Treanda (Bendamustine HCL) for Injection was approved on March 20, 2008 under NDA 022249. On March 8, 2013, the Applicant submitted manufacturing Supplement 015 for a new dosage form, (b) (4) injection.

On June 14, 2013 The Center for Medicine in the Public Interest (CMPI) submitted a Citizen Petition requesting the FDA refrain from approving a new drug application or supplemental new drug application for Treanda (b) (4) until certain conditions are satisfied. Namely, the petition requests the Applicant demonstrate the new formulation impurity profile is within acceptable limits, demonstrate safety of excipients and safe use of new strength.

1.2 PRODUCT INFORMATION

The following product information is provided in prior approval Supplement 015 dated March 8, 2013.

- Active Ingredient: Bendamustine
- Indication of Use: indicated for treatment of patients with chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen.
- Route of Administration: Intravenous
- Dosage Form: (b) (4)
- Strength: 45 mg per 0.5 mL and 180 mg per 2 mL
- Dose and Frequency:
    - Chronic lymphocytic leukemia: 100 mg/m2 infused intravenously over 30 minutes on Days 1 and 2 of 28 day cycle, up to 6 cycles.
    - Non-Hodgkin's Lymphoma (NHL): 120 mg/m2 infused intravenously over 60 minutes on Days 1and 2 of a 21 day cycle up to 8 cycles.
- How Supplied: 2 mL glass vial
- Storage: store at 2°C to 8°C (36°F to 46°F) in original carton
- Container and Closure System: glass vial with (b) (4) (45 mg) or (b) (4) (180 mg) flip off cap.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Treanda medication error reports. We also reviewed the Treanda labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database from the date of the last DMEPA search using the strategy listed in Table 1. See Appendix A for a description of the FAERS database.

Table 1: FAERS Search Strategy	
Date	July 31, 2012 to April 24, 2013
Drug Names	Bendamustine (active ingredient) Bendamustine Hydrochloride (active ingredient)
MedDRA Search Strategy	Medication Errors HLGT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 14 cases. Each case was reviewed for relevancy and duplication. After individual review, 12 cases were not included in the final analysis for the following reasons:

- Accidental exposure
- Foreign cases
- Product Quality Issues
- Off label use
- Errors unrelated to Treanda

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 21, 2013 (Appendices B and C)
- Carton Labeling submitted June 21, 2013 (Appendices D and E)
- Insert Labeling submitted March 8, 2013

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

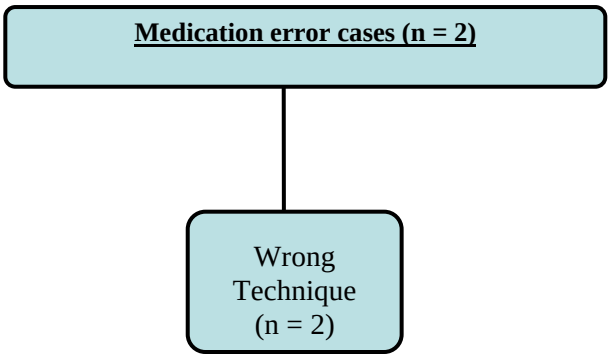
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the (b) (4) product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, two Treanda medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error.

Figure 1: Treanda medication errors (n = 2) categorized by type of error



Wrong Technique (n = 2)

Two cases (Case# 9109752 v1, Case# 8902979 v1) described wrong technique errors occurring during the reconstitution of Treanda. Both cases described the reconstitution of Treanda with 0.9% Sodium Chloride USP instead of Sterile Water for Injection, USP,
The insert labeling clearly states that the lyophilized powder can only be reconstituted with sterile water for injection and further dilution of the drug prior to administration should be in 0.9% Sodium Chloride USP or 0.45% Sodium Chloride/2.5% Dextrose prior to intravenous administration.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

1. Response to Citizen's Petition regarding safety concerns with the Proposed New Strength

   The Division of Medication Error Prevention and Analysis (DMEPA) acknowledges the Petitioner's concern regarding the safe use of Treanda with the change in concentration as stated in the Citizen's Petition dated June 14, 2013. These safety concerns will be mitigated thru revisions to the container label and carton labeling, as well as the sponsor commitment to implement an educational program.

2. Review of the Proposed Container Label and Carton Labeling

   A review of the proposed (b) (4) labels and labeling indicates the expression of strength in terms of (b) (4) However, the United States Pharmacopeia (USP) General Chapter <1> Injections labeling standard requires the labeling of all injectable liquid products present the total drug content and strength in a consistent manner. The strength per total volume (i.e., the total milligrams of Bendamustine HCl per total number of milliliters) should be the primary and most prominent expression on the principle display panel of the label, followed in close proximity by strength per milliliter enclosed by parentheses (i.e., milligrams of Bendamustine HCl per milliliter). Presenting the total drug content and strength per mL as required by the USP may help prevent practitioners from misinterpreting the total drug content of the vial, and thus decrease the risk of medication errors. Therefore, we recommend the proposed labels and labeling conform to the United States Pharmacopeia (USP) General Chapter <1> Injections labeling standard.

3. Comments on the Proposed New Formulation, (b) (4)

   We note that the change in formulation has changed the storage requirements from storage at room temperature to storage under refrigeration for Treanda. This is an important change that should be communicated to the end user. We recommend relocating the statement on storage to be prominently displayed on the principal display panel. Next, we considered whether the proposed dosage form, (b) (4) injection, was an approved CDER dosage form. We inquired to the Office of New Drug Quality Assessment (ONDQA) to determine the correct dosage form for this product. The ONDQA reviewer stated the correct dosage form is "injection".

4 CONCLUSIONS

DMEPA concludes that the proposed label container, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product and mitigate any confusion associated with the presentation of the strength.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this supplement:

A. Insert labeling

1. Revise the statement of strength (e.g. [redacted (b) (4)]) to read (45 mg/0.5 mL and 180 mg/2 mL) throughout the insert labeling.

B. Container Labels

1. Ensure the proprietary name, Treanda, appears in title case (e.g. Treanda)
2. Revise the highlighted [redacted (b) (4)] color box displaying the strength statement to incorporated the entire strength statement on the 180 mg/2 mL to appear similar to:

180 mg/2 mL
(90 mg/mL)

3. Debold the statement "Rx Only" and relocate the statement to the lower one-third of the principle display panel (pdp).
4. Ensure the text is presented in a horizontal orientation to the normal storage orientation of the container.
5. Add the statement "Single Dose Vial" to the side panel of the container label. If space permits add the statement "Discard Unused Portion" immediately following the statement "Single-Dose Vial". If additional space is needed then delete the two lines of text and numbers directly under the bar code, because these statements add clutter to the label and do not provide any valuable information to a healthcare provider.

C. Carton Labeling

1. Ensure the carton labeling complies with recommendations B1.
2. Revise the statement reading "[redacted (b) (4)]" to read "New Concentration and Storage Information" as this is more important information to convey to the end user. Ensure this statement does not appear on the labeling for longer than 6 months.
3. We recommend displaying the statement "Refrigerate" in bold font on the principal display panel to communicate the need for refrigeration with this new injection formulation.
4. Revise the highlighted [redacted (b) (4)] color box displaying the strength statement to incorporated the entire strength statement on the 180 mg/2 mL to appear similar to:

180 mg/2 mL
(90 mg/mL)

5. Debold the "Rx Only" statement appearing on the carton labeling.

6. Revise the statement "(b) (4)" to read "Single-Dose Vial". Relocate the statement and "Discard Unused Portion" to appear below the statement, "Further dilution is required".

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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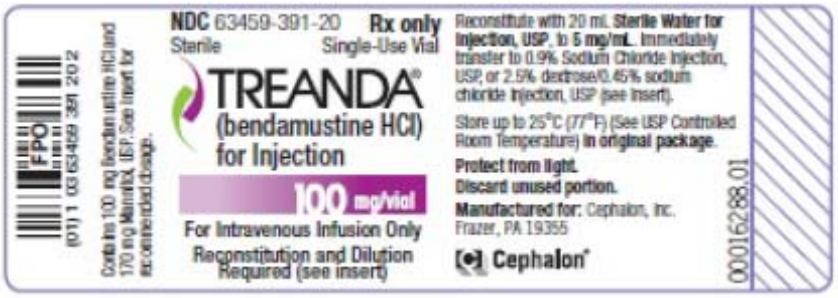
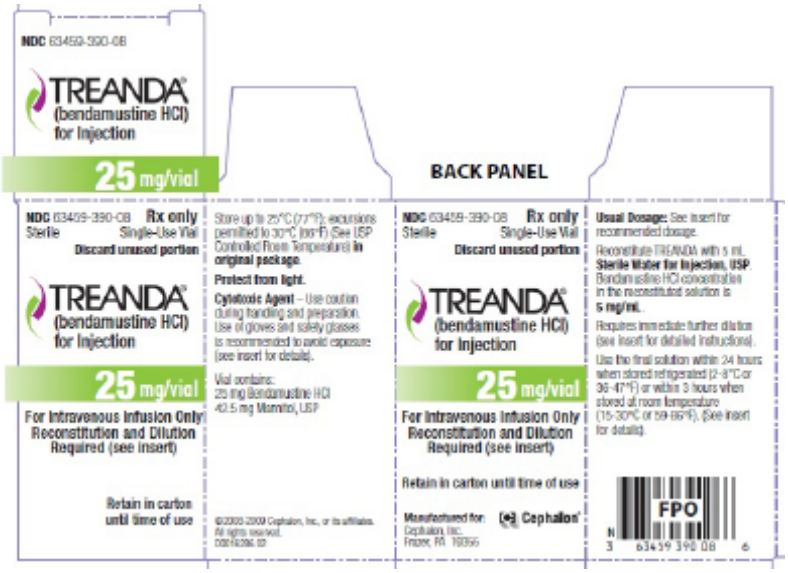
Appendix F: Container Labels (25 mg/vial)

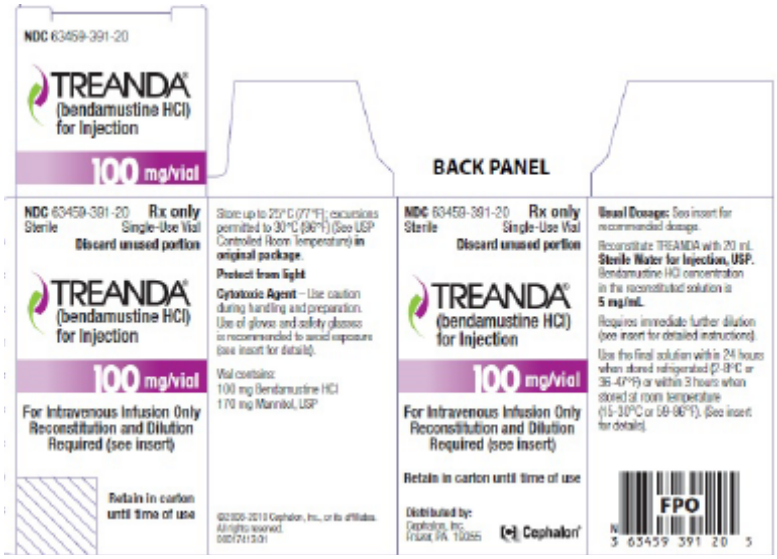
Appendix G: Container Labels (100 mg/vial)



Appendix H: Carton Labeling (25 mg/vial)



Appendix I: Carton Labeling (100 mg/vial)



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/s/

KEVIN WRIGHT
06/27/2013

JAMES H SCHLICK
06/28/2013

SCOTT M DALLAS
06/28/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Packaging Memorandum

July 2, 2013

Reviewer:	Kevin Wright, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Treanda (Bendamustine) Injection 45 mg per 0.5 mL and 180 mg per 2 mL (90 mg per mL)
Application Type/Number:	NDA 022249
Submission Number:	S-015
Applicant/sponsor:	Teva Pharmaceutical USA, Inc.
OSE RCM #:	2013-694-1

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 Introduction 1
2 Methods and Materials Reviewed 1
2.1 Labels and Labeling 1
2.2 Previously Completed Reviews 1
3 Conclusions 1
Appendices 2

1 INTRODUCTION

This review evaluates the revised container label, carton, and insert labeling for Treanda (Bendamustine) Injection, NDA 022249 submitted in response to the Division of Medication Error Prevention and Analysis' comments in June 28, 2013 OSE Review 2013-694.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 28, 2013 (Appendices A through B)
- Carton Labeling submitted June 28, 2013 (Appendices C though D)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed Treanda (Bendamustine) Injection in OSE Review# 2013-694, and we looked at that review to ensure all our recommendations were implemented. All the revisions to the container label, carton and insert labeling were implemented.

3 CONCLUSIONS

DMEPA finds the Applicant's revisions to the container label, carton and insert labeling acceptable.

If you have further questions, please contact Sue Kang, OSE project manager, at 301-796-4216.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

KEVIN WRIGHT
07/02/2013

JAMES H SCHLICK
07/02/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 27, 2013
To:	Ann Farrell, M.D., Acting Director, Division of Hematology Products
From:	Richard Pazdur, M.D. Director, Office of Hematology and Oncology Products (OHOP) Kevin Wright, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis Office of Medication Error Prevention and Risk Management
Through:	Yelena Maslov, Pharm.D., Team Leader Carol Holquist, R.Ph. Director, Division of Medication Error Prevention and Analysis Office of Medication Error Prevention and Risk Management Office of Surveillance and Epidemiology
Subject:	Treanda Injection, Potential Medication Errors Caused by Higher Concentration in Liquid Formulation
Drug Name(s):	Treanda (bendamustine hydrochloride) for injection, for intravenous infusion
OSE RCM #/	2013-1501
Application Type/Number	NDA 22-249

1 INTRODUCTION

This memo responds to a June 26, 2013, consult request from the Division of Hematology Products in the Office of Hematology and Oncology Products (DHP/OHOP) regarding potential medication errors caused by a higher concentration of the liquid formulation of bendamustine hydrochloride as compared to the reconstituted lyophilized powder formulation currently marketed as Treanda for injection, pursuant to NDA 22-249. This memo to file supports the approvability decision by DHP/OHOP for NDA 22-249, CMC supplement 015.

DHP will be responding to a citizen petition submitted by petitioner, the Center for Medicine in the Public Interest, regarding Treanda for Injection. The Petitioner requests that FDA refrain from approving any NDA or sNDA for a liquid formulation of Treanda until, (among other actions) the applicant demonstrates that significant dosing errors will not occur with the liquid formulation due to different dilution requirements than the lyophilized product.

The bulleted questions (printed in bold), numbered A, B, and C, are based on the DHP consult memo. OSE responses are printed below the question.

2 OSE RESPONSE TO QUESTIONS POSED BY DHP/OHOP

Question A

Have there been reports of adverse events related to dilution errors with the lyophilized formulation of Treanda?

No adverse events were reported following errors of reconstitution of Treanda lyophilized powder with the wrong diluent.

Question B

Petitioner claims that the difference in concentration of bendamustine HCl in the liquid product versus the lyophilized product will lead to dosing errors if one formulation is mistakenly used in place of the other. Is that a valid concern? Why or why not? Has the issue been addressed in the labeling and any related prescriber information?

Errors in dosing may result if one formulation is mistakenly used in place of the other. However, these concerns are not unique to Treanda. The following measures are being taken to minimize product selection errors between the lyophilized powder and liquid formulations of Bendamustine HCL:

- Different color schemes are used to distinguish the labels and labeling of the solution from the lyophilized product.
- The solution for injection label expresses the statement of strength in terms of total drug content per total volume [i.e. 180 mg/2 mL (90 mg/mL) and 45 mg/0.5 mL) respectively] whereas the lyophilized powder label expresses the strength in terms of total drug content per vial (i.e. 100 mg/vial).
- A bolded statement "New Concentration and Storage Information" appears in a colored banner on the top of the carton labeling.
- A prominent statement "Refrigerate" appears in the upper part of the carton labeling.
- The applicant changed the vial size and volume to be extracted from the vial.

Additionally, the applicant states that (b) (4) and an education program. However, we have no details on the specific (b) (4) and administration process.

Question C

Petitioner requests a failure mode and effects analysis to mitigate the risk of unintentional overdose or other medication errors due to differences between the liquid and lyophilized formulations of Treanda. Is such an analysis necessary? Why or why not?

A Failure Mode and Effects Analysis is not required for approval of this supplement. However, such a proactive risk assessment can help to identify additional labeling enhancements that may minimize product confusion with the introduction of the new liquid formulation. We do not know if the Applicant conducted a risk assessment prior to submission. However, the Applicant proposed the following strategy to minimize the risk of confusion in their submission:

- Change in the color of carton labeling and container label to have distinctive appearance.
- Change in vial size and volume to be extracted, so it will be impossible to replicate the original administration.

- (b) (4)
- .

Based on information provided in the submission and after internal discussion within the Agency, it was determined that the proposed strategies to minimize medication errors related to the change in product formulation were adequate.

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/s/

KEVIN WRIGHT
09/12/2013

YELENA L MASLOV
09/12/2013

CAROL A HOLQUIST
09/13/2013

REGULATORY PROJECT MANAGER LABELING REVIEW

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I

Application Number: NDA 22249/S-015

Name of Drug: Treanda (bendamustine HCl) Injection

Applicant: Teva Pharmaceuticals Inc.

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Content of Labeling (SPL)	6/21/2013	6/21/2013	Last approved label 8/28/13 – S014
Carton and Container Labels	8/9/2013	8/9/2013	Last approved label 3/20/08 – Orig. NDA

Background and Summary

On March 8, 2013, Teva Pharmaceuticals Inc. submitted a Prior Approval Supplement that proposes a new liquid formulation to replace the existing lyophilized formulation of Treanda. This supplement is changing the formulation from a lyophilized powder to a ready to mix solution, so labeling and the resulting strength are different from what was originally approved in March 20, 2008. While there is a difference formulation, the product is essentially the same.

This supplement was initially managed by the OND clinical division.
A DMEPA consult was issued on June 26, 2013. On July 2, 2013, DMEPA found changes to the Carton and Container labeling acceptable after requested revisions (by DMEPA) were made (see reviews June 28, 2013 and July 2, 2013). However, a Complete Response action was taken due to Product Quality Issues on July 2, 2013. Teva resubmitted their supplement on July 26, 2013 and included revised content labeling. This resubmission was managed by ONDQA at the request of the OND clinical division.

Review

This comparison was done by visually comparing the proposed to the last submitted or approved labeling on file.

The following are the assessments for each change identified:

Content of Labeling:

Changes made were requested by the clinical division on June 27, 2013.

Comment: Changes are acceptable per clinical division.

Immediate Container Label and Carton Label:

1. All the revisions to the container and carton label were implemented as per DMEPA review and recommendations from June 28, 2013. Container and carton labels for the 180mg/2mL and 45mg/0.5mL formulations are complete and contain all mandatory requirements.

Comment: Acceptable per DMEPA Review July 2, 2013.

Recommendations

This supplement is recommended for approval.

Jewell Martin
Regulatory Project Manager
Office of New Drug Quality Assessment Date 9/12/2013

Michael Folkendt
Supervisory Regulatory Project Manager Date 9/12/2013
Office of New Drug Quality Assessment

Following this page, 15 pages withheld in full - (b)(4) draft labeling

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/s/

JEWELL D MARTIN
09/12/2013

MICHAEL M FOLKENDT
09/13/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22249/S-015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Cephalon
deliver more

www.cephalon.com

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355
Phone 610-344-0200
Fax 610-344-0065

March 8, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0062
TREANDA® (bendamustine hydrochloride) for Injection:
Prior Approval CMC Supplement
Request for Priority Review

Dear Dr. Farrell:

Reference is made to the approval letter for NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection dated March 20, 2008. Reference is also made to the approval of supplement S001, dated May 1, 2009, for the 25 mg vial, and to approval of supplement S007, dated August 13, 2010, for an alternate manufacturing site.

The purpose of the submission of this Prior Approval Supplement is to propose replacement of the existing lyophilized formulation of Treanda. Treanda is currently approved as a single-use vial containing either 25 mg/vial or 100 mg/vial of bendamustine hydrochloride as a lyophilized powder that is reconstituted with Sterile Water for Injection, USP. The proposed new formulation will be a single-use vial containing either 45 mg/vial or 180 mg/vial of bendamustine hydrochloride as a sterile solution formulation that contains inactive ingredients that have previously been FDA-approved for use in commercial products. There is no change to the actual administration of the new formulation since it will still be aseptically withdrawn and transferred into a 500 mL infusion bag of either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection to produce the same concentration as the original formulation prior to intravenous infusion. There is no change in the bendamustine HCl drug substance. Differences in bioavailability are not expected in humans based on the demonstrated lack of difference in pharmacokinetics between the two formulations in monkeys.

The development of this formulation was prompted during the commercialization of Treanda when dilution errors were reported. At the time of this filing, there have been no reports of infusion related adverse events resulting from these errors, but over 150 product complaints have been received where many of the reporters described the diluted product as being cloudy or not clear. We were unable to test most of these vials, but about a third of the reports stated they incorrectly reconstituted with saline. This could be the cause of the cloudy appearance since bendamustine HCl is not completely solubilized in saline. Due to the fact that the reconstituted product is injected into a 500 mL infusion bag, we believe that diluent-related adverse events have been avoided;

however, the need for a liquid formulation has been a target for improved development of the product.

Due to the referenced dilution errors, we are requesting priority review of the supplement since Teva supports that the proposed liquid formulation is an improvement in the administration of the product that would eliminate reconstitution errors and potentially reduce the risk of exposure among pharmacy and nursing staff who currently have contact with the product vials containing the lyophilized powder formulation. The Request for Biowaiver included with this submission provides additional information regarding dilution errors and reported events of exposure to the bendamustine lyophilized formulation.

The safe transition to a new formulation for any product is paramount when a replacement strategy is undertaken. Therefore, at the time of approval of the supplement, Teva will propose a (b) (4)

In support of this supplement, we are including a new Drug Product section in Module 2 and 3, revised labeling and patent information for the new formulation, a basis for submission statement, a biowaiver request, and other pertinent sections of the NDA.

We will be submitting a request for (b) (4) to the NDA under a separate cover.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on March 8, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-3411 or via email at Sherri.Carenzo@tevapharm.com. For questions relating to the CMC section of this submission, please contact either Shirley Speer at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com, or Sylvie Peltier at (610) 727-6152 or via email at Sylvie.Peltier@tevapharm.com.

Sincerely,

Sherri Carenzo
Manager
Regulatory Affairs

Branded Pharmaceutical Products R&D

March 22, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0064
TREANDA® (bendamustine hydrochloride) for Injection:
Amendment to Pending Application:
Revised Labeling Components

Dear Dr. Farrell:

Reference is made to our New Drug Application 22-249 for TREANDA® (bendamustine hydrochloride) for Injection dated March 20, 2008, to our pending Prior Approval Supplement for a new liquid formulation of TREANDA, submitted March 8, 2013 (Sequence No. 0062), and to our pending (b) (4)

The purpose of this submission is to replace the proposed labeling components for the 45 mg and 180 mg carton and vial. The proposed container and carton labeling included with our original sNDA application was a marked-up version with changes to be incorporated. The revised container and carton labeling included with this submission incorporates those changes for easier review.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on March 22, 2013 by Teva Branded Pharmaceutical Products R&D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-3411 or via email at Sherri.Carenzo@tevapharm.com.

Sincerely,

Sherri Carenzo
Manager
Regulatory Affairs

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel 610.344.0200 | Fax 610.783.6311 | www.tevapharm-na.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22249/S-015

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT (CMC)

Cephalon, Inc., a wholly owned subsidiary of Teva Pharmaceutical Industries, Ltd.
Attention: Sherri Carenzo
Manager, Regulatory Affairs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Dear Ms. Carenzo:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 22249

SUPPLEMENT NUMBER: 015

PRODUCT NAME: TREANDA® (bendamustine hydrochloride)
Lyophilized Solid for Injection, 25 mg/vial; 100 mg/vial

DATE OF SUBMISSION: March 8, 2013

DATE OF RECEIPT: March 8, 2013

This supplemental application proposes the following change(s): a new liquid formulation of TREANDA® in a single use vial containing 45 mg/vial or 180 mg/vial of bendamustine hydrochloride.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 7, 2013, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **July 8, 2013**.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Theresa A. Carioti, MPH
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

THERESA A CARIOTI
04/10/2013

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

April 26, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0065
TREANDA® (bendamustine hydrochloride) for Injection:
Amendment: Prior Approval CMC Supplement S-015
Response to FDA Request for Information

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8th, 2013. Further reference is made to an April 25th teleconference with Jewell Martin, Regulatory Health Project Manager.

The purpose of this amendment is to provide the site contact information for the manufacturing, packaging, labeling and testing sites for Treanda (bendamustine HCl) (b) (4) Injection. The contact information is provided in the 356h form. In addition, section 3.2.P.3.1 has been updated to include the city, state and zip code information for Teva Pharmaceuticals located at 145 Brandywine Parkway.

The following is the contact information for the manufacturing, packaging, labeling and testing facilities involved in the manufacture of Treanda (bendamustine HCl) (b) (4) Injection.

- Baxter Oncology GmbH, Kantstrasse 2, 33790 Halle/Westphalia, Germany
  Contact: (b) (6)
  Phone:
  e-mail:

- (b) (4)
  Contact:
  Phone:

- Teva Pharmaceuticals, 145 Brandywine Parkway, West Chester, PA 19380
  Contact: Barry Brooks, Senior Director, Supply Chain Quality Assurance

Phone: 215-591-8685, Cell: (b) (6) Fax: 610-738-6750,
e-mail: barry.brooks@tevapharm.com

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on April 26, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Sherri Carenzo at (610) 727-3411 or via email at Sherri.Carenzo@tevapharm.com.

Sincerely,

Shirley Speer
Sr. Manager
Regulatory Affairs, CMC

Carioti, Theresa

From: Carioti, Theresa
Sent: Wednesday, May 01, 2013 5:10 PM
To: 'Sherri Carenzo'
Subject: NDA 22249/S-015 Treanda liquid formulation - Biopharm Info Request - Respond by May 10 COB
Importance: High

Dear Sherri,
Please refer to NDA 22249/S-015 that proposes a new liquid formulation for Treanda. This prior approval CMC supplement is under review and we have the below biopharmaceutics information request.

Information Request

As per 21 CFR § 320.22 (b), FDA shall waive the requirement for submission of demonstrating bioequivalence if the drug product is a parenteral solution for injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. In addition, your product should have similar pH, tonicity and osmolarity to the approved product. Therefore, FDA shall not grant biowaiver for demonstration of bioequivalence unless your proposed product has similar concentration, pH, tonitciy and osmolarity to the approved product unless you submit justification on the lack of clinical relevance of the proposed variations on these parameters including the absence of mannitol. Therefore, please provide information/justification supporting that the in vivo physiological disposition of Bendamustine hydrochloride from your proposed product formulated without mannitol will not be different than that of the approved product.

Please provide a written response (via email) to the information request by **Friday, May 10, 2013 COB.** Please also follow-up with an official submission to the sNDA file.

Kindly confirm receipt of this email correspondence. Thank you.

Regards,
Theresa

Theresa A. Carioti, MPH
Regulatory Project Manager
Division of Hematology Products, OHOP, CDER, FDA
email: Theresa.Carioti@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A CARIOTI
05/01/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 22249 **Applicant: Cephalon** **Stamp Date: March 8, 2013**

Drug Name: Treanda (bendamustine HCl) **NDA Type: CMC prior approval supplement**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	**X**		The submission is in eCTD format.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	**X**		Electronic submission.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	**X**		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	**X**		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	**N/A**		The Applicant is changing from a lyophilized drug product that is reconstituted in sterile water and further diluted in saline for intravenous to a nonaqueous solution. A single-dose study in pharmacokinetic study in cynomolgus monkeys was conducted to compare the lyophilized drug product with the nonaqueous solution product.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	**X**		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	**X**		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	**X**		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	**X**		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	**X**		This is a review issue. A 15-week intermittent infusion study was conducted in rats to evaluate the effects of the new nonaqueous solution and to qualify the presence of 2 propylene glycol esters ((b) (4) (b) (4) and (b) (4)) that are degradation products formed during drug product storage.
11	Has the applicant addressed any abuse potential issues in the submission?	**N/A**		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	**N/A**		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Christopher M. Sheth, Ph.D. 05/02/2013
Reviewing Pharmacologist Date

Haleh Saber, Ph.D. 05/02/2013
Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

CHRISTOPHER M SHETH
05/02/2013

HALEH SABER
05/02/2013

From: Martin, Jewell
To: "Sherri Carenzo"
Cc: Shirley Speer; Carioti, Theresa
Subject: RE: Teva Teleconference w/CMC Team - List of Questions/Attendees
Date: Friday, May 03, 2013 10:19:00 AM
Attachments: image001.png

Hello Sherri,

Thank you for the call in information. Please find a list of tentative meeting attendees below as well as the issues to be discussed at the TCON.

Tentative Meeting Attendees:
Hasmukh B Patel, Branch Chief, ONDQA
Sue Ching Lin, CMC Reviewer, ONDQA
Theresa Carioti, Regulatory Project Manager, OND
Jewell Martin, Regulatory Project Manager, ONDQA

The purpose of the meeting is to discuss the following issues:

1. Drug product composition (Section 3.2.P.1): For a solution, the drug product strength should be expressed as weight/volume (e.g., 45 mg/ 0.5 mL, 180 mg/ 2 mL), instead of (b) (4). The composition should be based on the actual volume obtained from the manufacturing process. Please refer to issue #2 below. Provide unit and batch composition in a tabular format.

2. Manufacturing process (Section 3.2.P.3.3):

   This process does not appear to be able to (b) (4) .

3. (b) (4)

4. Section (b) (4) of the package insert (b) (4) states to (b) (4) . This statement is not correct as it is not (b) (4)

5. The submitted stability data (b) (4)

6. For the supportive stability batch, please indicate whether (b) (4) production.

7. The compatibility study section (Section 3.2.P.2.6) is not adequate. Please

provide testing results for [redacted] (b) (4)

8. The concentration of the solution as stated on the labeling (90 mg/mL) appears to be very different from that of the reconstituted solution for Treanda (which is 5 mg/ mL). There is a concern for medication errors that may arise due to this high a concentration.

Best,

Jewell

From: Sherri Carenzo [mailto:Sherri.Carenzo@tevapharm.com]
Sent: Thursday, May 02, 2013 5:48 PM
To: Martin, Jewell
Cc: Shirley Speer; Carioti, Theresa
Subject: Teva Teleconference w/CMC Team - List of Questions/Attendees

Hi Jewell,

We were wondering if we will still be receiving the questions/topics for discussion and list of FDA attendees by EOD today as discussed, ahead of tomorrow's teleconference scheduled for 2pm. This information will help ensure Teva has the appropriate team members in attendance.

Best regards,
Sherri

Sherri Carenzo
Manager
Regulatory Affairs, Oncology

Phone: (610) 727-3411
mailto:Sherri.Carenzo@tevapharm.com

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
Frazer, PA 19355

Mobile: [redacted] (b) (6)
Fax: (610) 786-7051

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/s/

JEWELL D MARTIN
06/12/2013

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www.cephalon.com

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355
Phone 610-344-0200
Fax 610-344-0065

May 6, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0066
TREANDA® (bendamustine hydrochloride) for Injection:
Response to FDA Request for Information
CMC Prior Approval Supplement-S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. Further reference is made to telephone and e-mail correspondence May 2-3, 2013, between Jewell Martin, FDA, Regulatory Health Project Manager and Sherri Carenzo, Teva Pharmaceuticals, Manager, Regulatory Affairs with FDA's CMC team requesting a teleconference with Teva and a list of issues for discussion. Reference is also made to the subsequent teleconference on May 3, 2013 between FDA and Teva to discuss those issues provided in the e-mail correspondence.

Prior Approval Supplement S-015 provides for a new liquid formulation of Treanda® in a single use vial to replace the currently approved lyophilized product formulation. The purpose of this submission is to provide written responses to FDA questions 1 through 3 discussed during the teleconference on May 3rd. Written responses to questions 4 through 8 will be provided to FDA in the near future.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on May 6, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Sherri Carenzo at (610) 727-3411 or via email at Sherri.Carenzo@tevapharm.com.

Sincerely,

Shirley Speer

Shirley Speer
Sr. Manager, Regulatory Affairs, CMC

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

May 10, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249/S-015; Sequence No. 0067
TREANDA® (bendamustine hydrochloride) for Injection:
Response to FDA Request for Information
Biopharmaceutics Information Request
CMC Prior Approval Supplement

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. Further reference is made to e-mail correspondence from Theresa Carioti, FDA, Regulatory Project Manager on May 1, 2013, requesting a written response to a biopharmaceutics request.

The purpose of this submission is to provide a response to FDA's request for information.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on May 10, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-3411 or via email at Sherri.Carenzo@tevapharm.com.

Sincerely,

for Sherri Carenzo
Manager
Regulatory Affairs

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

May 10, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0068
TREANDA® (bendamustine hydrochloride) for Injection:
Response to FDA Request for Information
CMC Prior Approval Supplement-S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. Prior Approval Supplement S-015 provides for a new liquid formulation of Treanda® in a single use vial to replace the currently approved lyophilized product formulation.

Reference is made to telephone and e-mail correspondence May 2-3, 2013, between Jewell Martin, FDA, Regulatory Health Project Manager and Sherri Carenzo, Teva Pharmaceuticals, Manager, Regulatory Affairs with FDA's CMC team requesting a teleconference with Teva and a list of issues for discussion. A teleconference was held on May 3, 2013 between FDA and Teva to discuss those issues provided in the e-mail correspondence. Reference is made to a Response to FDA Request for Information, Sequence 0066, submitted May 7th, 2013 to provide written response to questions 1 through 3 discussed during the teleconference.

The purpose of this submission is to provide written response to FDA questions 4 through 8 discussed during the teleconference on May 3rd, in addition to a question regarding Teva Pharmaceuticals as a testing site. Updates to the CTD sections that will require revisions as a result of these responses will be provided to FDA in the near future.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on May 10, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Sherri Carenzo at (610) 727-3411 or via email at Sherri.Carenzo@tevapharm.com.

Sincerely,

Shirley Speer

Shirley Speer
Sr. Manager, Regulatory Affairs, CMC

Carioti, Theresa

From: Carioti, Theresa
Sent: Monday, May 13, 2013 5:27 PM
To: Sherri Carenzo
Cc: Martin, Jewell
Subject: Treanda NDA 22249/ S-015 liquid formulation - Micro IR - Response requested by MAY 21 COB
Importance: High

Dear Sherri,
Please refer to Treanda, NDA 22249 / S-015 that proposes a new liquid formulation. We have the following microbiology information request.

Microbiology Information Request:

1. Your application describes use of a [redacted (b) (4)] Describe the [redacted (b) (4)] process for this [redacted (b) (4)]

2. Your application describes [redacted (b) (4)].
   More information is needed. Address the following points:
   a. [redacted (b) (4)]
   b. [redacted]

3. Your description of the manufacturing process states that the [redacted] (b) (4) Clarify the [redacted] for this drug product.

4. Your application describes [redacted] (b) (4). More information is needed. Address the following points:
   a. [redacted] (b) (4)
   b. [redacted]
   c. [redacted]

5. [redacted] (b) (4)

Please provide a written response (via email) to the information request by **Tuesday, May 21, 2013 COB.** Please also follow-up with an official submission to the sNDA file.

Kindly confirm receipt of this email correspondence. Thank you.

Regards,
Theresa

Theresa A. Carioti, MPH
Regulatory Project Manager
Division of Hematology Products, OHOP, CDER, FDA
email: Theresa.Carioti@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A CARIOTI
05/13/2013

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

May 21, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0070
TREANDA® (bendamustine hydrochloride) for Injection:
Response to FDA Microbiology Request for Information
CMC Prior Approval Supplement-S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. Prior Approval Supplement S-015 provides for a new liquid formulation of Treanda® in a single use vial to replace the currently approved lyophilized product formulation.

Reference is made to e-mail correspondence dated May 13, 2013, from Theresa Carioti, FDA, Regulatory Health Project Manager to Sherri Carenzo, Teva Pharmaceuticals, Manager, Regulatory Affairs requesting information on microbiology.

The purpose of this submission is to provide written response to FDA Microbiology Information Request, questions 1 through 5, provided in the above referenced e-mail correspondence. Updates to the CTD sections that will require revisions as a result of these responses will be provided to FDA in the near future.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on May 21, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Sherri Carenzo at (610) 727-3411 or via email at Sherri.Carenzo@tevapharm.com.

Sincerely,

Shirley Speer

Shirley Speer
Sr. Manager, Regulatory Affairs, CMC

From:	Carioti, Theresa
To:	Shirley Speer
Cc:	Sherri Carenzo; Martin, Jewell
Bcc:	Lin, Sue Ching
Subject:	NDA 22249/ S-015 Treanda - CMC Info Request: Please respond by 5/30/13 COB
Date:	Wednesday, May 22, 2013 2:57:00 PM
Importance:	High

Dear Shirley,
Please refer to NDA 22249 / S-015 submitted March 8, 2013 that proposes a new liquid formulation for Treanda. Please respond to the below CMC information request by next **Thursday, May 30, 2013 COB.**

Please update Module 3 with the revised CMC information that has been submitted in Module 1, Section 1.11 of all the CMC amendments of this supplement. It is noted that Module 3 has not been updated with the responses provided in the amendments.

Kindly confirm receipt of this email message. Thank you.

Regards,
Theresa

Theresa A. Carioti, MPH
Regulatory Project Manager
Division of Hematology Products, OHOP, CDER, FDA
email: Theresa.Carioti@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A CARIOTI
05/22/2013

From:	Carioti, Theresa
To:	"Shirley Speer"
Cc:	Sherri Carenzo; Martin, Jewell
Bcc:	Pfeiler, Erika
Subject:	NDA 22249 / S-015 Micro IR Treanda liquid formulation- Response requested by 6/4/13 COB
Date:	Tuesday, May 28, 2013 5:48:00 PM
Importance:	High

Dear Shirley,
Please refer to Treanda, NDA 22249 / S-015 that proposes a new liquid formulation. The prior approval supplement is under review and we have the following microbiology information request for which we ask for your response by **Tuesday, June 4, 2013 COB**.

Please send your written response via email to help expedite review and then follow with an official submission to the sNDA file.

Microbiology Information Request:

We acknowledge your 21 May 2013 submission in which you describe (b) (4) studies. You state that (b) (4), What are the (b) (4)? Which (b) (4) in these studies?

Please confirm receipt of this email message.

Thank you.

Regards,
Theresa

Theresa A. Carioti, MPH
Regulatory Project Manager
Division of Hematology Products, OHOP, CDER, FDA
email: Theresa.Carioti@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A CARIOTI
05/28/2013

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www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

May 30, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0072
TREANDA® (bendamustine hydrochloride) for Injection:
Response to Request for Information
CMC Prior Approval Supplement-S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. Additional reference is made Chemistry, Manufacturing and Controls (CMC) amendments dated May 6 (Seq. 0066), May 10 (Seq. 0068) and May 21 (Seq. 0070), 2013, which provided responses to FDA's request for information. Prior Approval Supplement S-015 provides for a new liquid formulation of Treanda® in a single use vial to replace the currently approved lyophilized product formulation.

Reference is made to e-mail correspondence dated May 22, 2013, from Theresa Carioti, FDA, Regulatory Health Project Manager to Shirley Speer, Teva Pharmaceuticals, Sr. Manager, Regulatory Affairs requesting updates to the Module 3 documents based on responses provided in the above referenced amendments.

The purpose of this submission is to provide the following updated documents with the revised CMC information based on the May 6th, May 10th and May 21st amendments to S-015:

- 2.3 – Introduction to the Quality Overall Summary
- 3.2.P.1 – Description and Composition of the Drug Product
- 3.2.P.2.2 – Drug Product
- 3.2.P.2.3 – Manufacturing Process Development
- 3.2.P.2.6 – Compatibility
- 3.2.P.3.1 – Manufacturer(s)
- 3.2.P.3.2 – Batch Formula
- 3.2.P.3.3 – Description of Manufacturing Process and Process Controls
- 3.2.P.3.5 – Process Validation and/or Evaluation
- 3.2.P.5.1 – Specifications
- 3.2.P.5.2 – Analytical Procedures
- 3.2.P.5.3 – Validation of Analytical Procedures
- 3.2.P.5.4 – Batch Analyses

- 3.2.P.5.6 – Justification of Specification(s)
- 3.2.P.8.1 – Stability Summary and Conclusion
- 3.2.P.8.2 – Post Approval Stability Protocol and Stability Commitment
- 3.2.P.8.2 – Stability Data

In addition to the updated CMC information, Section 1.3.1.2 is provided as notification of a change in sponsor contact information.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on May 30, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Michael McGraw at (610) 727-6136 or via email at Mike.McGraw@tevapharm.com.

Sincerely,

Shirley Speer

Shirley Speer
Sr. Manager, Regulatory Affairs, CMC

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

June 3, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0073
TREANDA® (bendamustine hydrochloride) for Injection:
Response to FDA Microbiology Request for Information
CMC Prior Approval Supplement-S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. Prior Approval Supplement S-015 provides for a new liquid formulation of Treanda® in a single use vial to replace the currently approved lyophilized product formulation. Additional reference is made to a response to microbiology request for information, Question 4, submitted May 21, 2013, as sequence 0070.

The purpose of this submission is to provide written response to FDA Microbiology Information Request provided in an e-mail correspondence dated May 28, 2013, from Theresa Carioti, FDA, Regulatory Health Project Manager to Shirley Speer, Teva Pharmaceuticals, CMC Regulatory Affairs.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on June 3, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Mike McGraw at (610) 727-6136 or via email at Mike.McGraw@tevapharm.com.

Sincerely,

Shirley Speer

Shirley Speer
Sr. Manager, Regulatory Affairs, CMC

From:	Carioti, Theresa
To:	Shirley Speer
Cc:	Mike McGraw; Martin, Jewell
Bcc:	Lin, Sue Ching; Wright, Kevin
Subject:	Treanda NDA 22249/ S-015 Info Request - response needed by June 12 COB
Date:	Wednesday, June 05, 2013 5:39:00 PM
Importance:	High

Hi Shirley,
Please refer to NDA 22249 / S-015 submitted and received on March 8, 2013 that proposes a new liquid formulation of Treanda. We have the following deficiencies/comments that need to be addressed.

Please provide a written response via email by next **Wednesday, June 12, 2013 COB**. In addition, please follow-up with an official submission to your sNDA.

1. The following comments pertain to the immediate container labels:

   a. Change the dosage form for the proposed formulation from "(b) (4) (b) (4)" to "injection." Refer to USP<1> for the nomenclature of injections. Furthermore, the proposed (b) (4). In addition, replace (b) (4) with 45 mg/0.5 mL and 180 mg/2 mL respectively and remove the (b) (4). Injectable drug products should be labeled primarily in terms of total amount (with prominent expression in bold characters), followed immediately by contents per mL indicated in parentheses. Therefore, revise the presentation of the drug name and strength to the following for the 180 mg/2 mL presentation:

   Trade Name
   (bendamustine HCl injection)
   180 mg/2 mL
   (90 mg/mL)

   For vials less then 1 milliliter, the strength per milliliter should not be included as per USP <1>. Therefore, the following presentation is recommended for the 45 mg/0.5 mL fill size:

   Trade Name
   (bendamustine HCl injection)
   45 mg/0.5 mL

   b. Include lot number on the vial label.

   c. Add "Further dilution is required" on the container label.

2. The following comments pertain to the carton labeling:

   a. See comment #1a above for the presentation of the drug name and strengths.

b. Add “Do not freeze” under storage condition.

c. Replace “Manufactured in Germany” with “Manufactured by Baxter Oncology GmbH, Halle/Westphalia, Germany.”

3. The following comments pertain to SPL Product Data Element (PDE):

a. Change “ (b) (4) to “injection, solution” (SPL dosage form #C42945). Therefore, the drug name and dosage form area would appear as follows:

Trade Name
bendamustine hydrochloride injection, solution

b. Provide the required quantity information for the inactive ingredients under the heading of “Strengths.”

4. (b) (4)

5.

6.

7.

8.

9. (b) (4)

Please confirm receipt of this email message. Thank you.

Regards,
Theresa

Theresa A. Carioti, MPH
Regulatory Project Manager
Division of Hematology Products, OHOP, CDER, FDA
email: Theresa.Carioti@fda.hhs.gov
phone: 301-796-2848

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/s/

THERESA A CARIOTI
06/05/2013

From: Carioti, Theresa
To: Mike McGraw
Cc: Shirley Speer; Martin, Jewell
Bcc: Lin, Sue Ching; Wright, Kevin
Subject: RE: Treanda NDA 22249/ S-015 Info Request - FDA clarification - Response needed by June 12
Date: Friday, June 07, 2013 11:39:00 AM

Dear Mike,
Please see our responses below that provide clarification to comments #1 and #3.

1a. FDA Response:
The Agency acknowledges your response to comment 1a regarding the presentation of strength on the 45 mg/0.5 mL vial. Please note the USP General Chapter <1> labeling standard for injectables was adopted to help mitigate the risk of medication errors. Presenting the strength per mL on vial sizes less than 1 mL may cause the end user to misinterpret the total drug content contained in the vial. Therefore, the Division of Medication Error and Prevention Analysis (DMEPA) continues to recommend you revise the container labels and carton labeling to conform with USP General Chapter <1> labeling standard for injectables.

We recommend the following presentation for the 45 mg/0.5 mL fill size:

Trade Name
(bendamustine HCl injection)
45 mg/0.5 mL

1b. FDA Response:
Your proposal to explore other means to differentiate these products is acceptable. Please resubmit the mock up labels and labeling to the Agency for review.

3. FDA Response:
It is acceptable to include changes in the PDE table when you submit final SPL. However, provide the updated information that you are going to include in the SPL PDE, e.g., the quantity of inactive ingredients

Regards,
Theresa

From: Mike McGraw [mailto:Mike.McGraw@tevapharm.com]
Sent: Thursday, June 06, 2013 10:05 AM
To: Carioti, Theresa
Cc: Shirley Speer; Martin, Jewell
Subject: RE: Treanda NDA 22249/ S-015 Info Request - response needed by June 12 COB

Dear Theresa,

We received your questions and would like some clarification on a few issues related to the labeling.

1. The question states that: For vials less than 1 milliliter, the strength per milliliter should not be included as per USP <1>. Therefore, the following presentation is recommended for the 45 mg/0.5 mL fill size:

Trade Name
(bendamustine HCl injection)
45 mg/0.5 mL

One of the purposes of the smaller vial size is to reduce the potential for waste when dosing patients with a relatively small body surface area. For example, if a patient was only required to receive 130 mg, then their dose could come from three of the smaller vials instead of wasting drug by using the larger vial size to prepare the patient's dose. (b) (4)

(b) (4)

We were also requested to remove the (b) (4). The (b) (4) are used to differentiate the two vial strengths and avoid confusion between them. Would it be acceptable to change the (b) (4) to a different (b) (4)? Alternatively, can we use a color bar or some other way of differentiation for the labeling?

3. We were also requested to revise the SPL PDE and provide the response by June 12. We anticipate that there may be other changes to the labeling (i.e., prescribing information) resulting from our labeling discussions in the coming weeks. We agree to make the requested changes, but will it be acceptable to include the changes when we submit the final SPL after approval of the supplement?

If you would like to discuss any of these issues, then please let me know if you would like to have a brief TC with the labeling team from Teva.

Regards,
Mike

Michael J. McGraw, PharmD, MS
Director
Regulatory Affairs

Mobile: (b) (6)
mailto:mike.mcgraw@tevapharm.com

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Rd.
Frazer, PA 19355

Phone: (610)727-6136
Fax: (215)619-3846

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/s/

THERESA A CARIOTI
06/07/2013

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

June 7, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0075
TREANDA® (bendamustine hydrochloride) for Injection
Response to FDA Pharmacology/Toxicology Request for Information
CMC Prior Approval Supplement-S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. Prior Approval Supplement S-015 provides for a new liquid formulation of Treanda® in a single use vial to replace the currently approved lyophilized product formulation.

The purpose of this submission is to provide written response to FDA Pharmacology/Toxicology Information Request provided in an e-mail correspondence dated June 5, 2013, from Theresa Carioti, FDA, Regulatory Health Project Manager to Michael McGraw, Director, Regulatory Affairs.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on June 7, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me. For questions related to CMC, please contact Shirley Speer at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com.

Sincerely,

Michael J. McGraw, PharmD, MS
Director, Regulatory Affairs
Office: 610-727-6136
Cell: (b) (6)
Fax: 610-786-7051
Email: mike.mcgraw@tevapharm.com

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

June 12, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0076
TREANDA® (bendamustine hydrochloride) for Injection:
Response to Labeling and CMC Comments
CMC Prior Approval Supplement-S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. Prior Approval Supplement S-015 provides for a new liquid formulation of Treanda® in a single use vial to replace the currently approved lyophilized product formulation.

The purpose of this submission is to provide written response to FDA labeling and CMC comments provided in an e-mail correspondence dated June 5, 2013 from Theresa Carioti, FDA, Regulatory Health Project Manager to Shirley Speer, Teva Pharmaceuticals, CMC Regulatory Affairs.

The following documents have been revised and are provided in this response:

- 1.14.1.1 – Draft Container Label 45 mg / 0.5 mL
- 1.14.1.1 – Draft Container Label 180 mg / 2 mL
- 1.14.1.1 – Draft Carton Label 45 mg / 0.5 mL
- 1.14.1.1 – Draft Carton Label 180 mg / 2 mL
- 3.2.P.2.4 – Container Closure System to provide additional information from the extractable and leachable studies.
- 3.2.P.5.1 – Specifications to provide format changes.
- 3.2.P.5.2 – Analytical Procedures for Identification, Assay and Degradation products to revise the calculation formula for assay.
- 3.2.P.6 – Reference Standards or Materials to provide referenced standards for degradation products (b) (4) and (b) (4).
- 3.2.P.7 – Container Closure System to include a reference to DMF (b) (4)
- Letters of Authorization for DMF (b) (4) and DMF (b) (4) with the correct NDA number (22-249).

The updated information that will be included in the SPL Product Data Element (PDE) is provided in this written response. The changes in the PDE table will be provided with the submission of the final SPL as agreed with the Agency in e-mail correspondence dated June 7, 2013.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on June 12, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Mike McGraw at (610) 727-6136 or via email at Mike.McGraw@tevapharm.com.

Sincerely,

Shirley Speer

Shirley Speer
Sr. Manager, Regulatory Affairs, CMC

From:	Carioti, Theresa
To:	Mike McGraw; Shirley Speer
Cc:	Martin, Jewell
Bcc:	Lin, Sue Ching; Chidambaram, Nallaperumal; Wright, Kevin
Subject:	NDA 22249 / S-015 CMC deficiencies - Response requested by June 21st 12pm
Date:	Monday, June 17, 2013 4:11:00 PM
Importance:	High

Dear Mike and Shirley,
Please refer to Treanda, NDA 22249 / S-015 which proposes a new liquid formulation of Treanda. The product quality review team has the following deficiencies. Please provide a written response via email by **Friday, June 21, 2013, 12pm**; and follow-up with a formal submission to the sNDA file.

1. (b) (4)
2.
3.
4.
5.

6. (b) (4)

7.

8.

Please confirm receipt of this email message. Thank you.

Regards,
Theresa

Theresa A. Carioti, MPH
Regulatory Project Manager
Division of Hematology Products, OHOP, CDER, FDA
email: Theresa.Carioti@fda.hhs.gov

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

/s/

THERESA A CARIOTI
06/17/2013

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

June 21, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products (HFD-150)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence No. 0077
TREANDA® (bendamustine hydrochloride) for Injection:
Response to CMC Information Request
CMC Prior Approval Supplement-S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval Supplement S-015, submitted March 8, 2013. This Prior Approval Supplement S-015 provides for a new liquid formulation of Treanda® in a single use vial to replace the currently approved lyophilized product formulation.

The purpose of this submission is to provide written response to FDA labeling and CMC comments provided in an e-mail correspondence dated June 17, 2013 from Theresa Carioti, FDA, Regulatory Health Project Manager to Shirley Speer, Teva Pharmaceuticals, CMC Regulatory Affairs and Michael McGraw, Teva Pharmaceuticals, Director, Regulatory Affairs.

The following documents have been revised and are provided in this response:

- 1.14.1.1 – Draft Container Label 45 mg / 0.5 mL
- 1.14.1.1 – Draft Container Label 180 mg / 2 mL
- 1.14.1.1 – Draft Carton Label 45 mg / 0.5 mL
- 1.14.1.1 – Draft Carton Label 180 mg / 2 mL
- (b) (4)

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on June 21, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Michael McGraw at (610) 727-6136 or via email at Mike.McGraw@tevapharm.com.

Sincerely,

Shirley Speer
Sr. Manager, Regulatory Affairs, CMC

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

June 26, 2013

Ann Farrell, MD, Directo
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence 0078
TREANDA® (bendamustine hydrochloride) for Injection
Response to CMC and Labeling Information Request
CMC Prior Approval Supplement S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) for Injection, Prior Approval supplement S-15, submitted on March 8, 2013. This Prior Approval Supplement S-015 is to request approval for a new liquid formulation in a single use vial to replace the currently approved lyophilized product formulation. Reference is also made to Theresa Carioti, Lead Regulatory Project manager's email of June 26, 2013.

The purpose of this submission is to provide a written response to FDA labeling and CMC comments:

Question 1: Revise the admixture stability information to read " Use the final solution [redacted] (b) (4)
See insert for details"

Question 2: Delete '[redacted] (b) (4)' from the storage statement.

Question 3: Container labels

1. Ensure the proprietary name, Treanda, appears in title case (e.g. Treanda)
2. Debold the statement "Rx Only" and relocate the statement to the lower one-third of the principle display panel (pdp).
3. Ensure the text is presented in a horizontal orientation to the normal storage orientation of the container.
4. If space permits, add the statements "Single – Dose Vial, Discard Unused Portion.

Question 4 Carton Labeling

5. Ensure the carton labeling complies with recommendations B1.
6. Revise the statement reading '(b) (4) to read "New Concentration and Storage Information" as this is more important information to convey to the end user. Ensure this statement does not appear on the labeling for longer than 6 months.
7. We recommend placing the following storage statement on the principal display panel to communicate the need for refrigeration with this change in formulation. Therefore, we recommend that the following storage statement be displayed prominently in bold font on the pdp of the carton labeling, "Refrigerate".
8. Debold the "Rx Only" statement appearing on the carton labeling
9. Relocate the statement "Single – Dose Vial" and "Discard Unused Portion" to appear below the statement, "Further dilution is required".

The revised carton and label will be submitted tomorrow early afternoon.

Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 2.0 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 10.5.2328, antivirus engine 9.700.1001, virus pattern 14.11 with a release date of 6/25/2013 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at 610 727 6136.

Would you have any question, please do not hesitate to contact me at 610 727 6152 or via email at sylvie.peltier@tevapharm.com.

Sincerely,

Peltier

Sylvie Peltier, PharmD

Senior Director Regulatory CMC

Branded Pharmaceutical Products R&D

June 27, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence 0079
TREANDA® (bendamustine hydrochloride) Injection
Response to Information Request
CMC Prior Approval Supplement S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) Injection, Prior Approval supplement S-015, submitted on March 8, 2013. This Prior Approval Supplement S-015 is to request approval for a new liquid formulation in a single-use vial to replace the currently approved lyophilized product formulation.

The purpose of this submission is to provide written response to a question provided in an e-mail correspondence dated June 26, 2013 from Theresa Carioti, FDA, Regulatory Health Project Manager to Michael McGraw, Teva Pharmaceuticals, Director, Regulatory Affairs.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on June 27, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me. For questions related to CMC, please contact Shirley Speer at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com.

Sincerely,

Michael J. McGraw, PharmD, MS
Director, Regulatory Affairs
Office: 610-727-6136
Cell: (b) (6)
Fax: 610-786-7051
Email: mike.mcgraw@tevapharm.com

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. 610.344.0200 | Fax 610.344.0065 | www.tevapharm-na.com

Branded Pharmaceutical Products R&D

June 27, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence 0080
TREANDA® (bendamustine hydrochloride) Injection
Response to CMC and Labeling Information Request
CMC Prior Approval Supplement S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) Injection, Prior Approval supplement S-15, submitted on March 8, 2013. This Prior Approval Supplement S-015 is to request approval for a new liquid formulation in a single use vial to replace the currently approved lyophilized product formulation. Reference is also made to a response to a CMC and Labeling Information Request submitted June 26, 2013, Sequence 0078.

The purpose of this submission is to provide the revised carton and container labeling per FDA request.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on June 27, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me. For questions related to CMC, please contact Shirley Speer at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com.

Sincerely,

Michael J. McGraw, PharmD, MS
Director, Regulatory Affairs
Office: 610-727-6136
Cell: (b) (6)
Fax: 610-786-7051
Email: mike.mcgraw@tevapharm.com

Branded Pharmaceutical Products R&D

June 28, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence 0081
TREANDA® (bendamustine hydrochloride) Injection
Response to Information Request
CMC Prior Approval Supplement S-015

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) Injection, Prior Approval supplement S-015, submitted on March 8, 2013. This Prior Approval Supplement S-015 is to request approval for a new liquid formulation in a single-use vial to replace the currently approved lyophilized product formulation.

The purpose of this submission is to provide written response to a question provided in an e-mail correspondence dated June 28, 2013 from Theresa Carioti, FDA, Regulatory Health Project Manager to Michael McGraw, Teva Pharmaceuticals, Director, Regulatory Affairs.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on June 28, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me. For questions related to CMC, please contact Shirley Speer at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com.

Sincerely,

Michael J. McGraw, PharmD, MS
Director, Regulatory Affairs
Office: 610-727-6136
Cell: (b) (6)
Fax: 610-786-7051
Email: mike.mcgraw@tevapharm.com

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. 610.344.0200 | Fax 610.344.0065 | www.tevapharm-na.com

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

July 26, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence 0082
TREANDA® (bendamustine hydrochloride) Injection
RESUBMISSION - CMC Prior Approval Supplement S-015 (b) (4)
COMPLETE RESPONSE

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) Injection, Prior Approval Supplement S-015, submitted on March 8, 2013. This Prior Approval Supplement is to request approval for a new liquid formulation of TREANDA in a single-use vial to replace the currently approved lyophilized product formulation. Reference is also made to the Complete Response Letter (CRL) dated July 2, 2013 and to subsequent e-mail correspondence from Jewell Martin, Regulatory Project Manager, Office of New Drug Quality Assessment (ONDQA), dated July 18, 2013. Additional reference is made to (b) (4) , was found unacceptable.

Pursuant to 21 CFR 314.110(b)(1), the Applicant hereby submits a complete response to all of the specific deficiencies that the Agency has identified in the CRL referenced above. This resubmission fully addresses all the deficiencies listed.

PRODUCT QUALITY

The CRL referenced above states that " (b) (4) ' As explained in e-mail correspondence from the Applicant to FDA on July 3, 2013, Report Number DD-2008-059 was submitted as a General Correspondence to NDA 22-249 on August 27, 2008 to fulfill post marketing commitment (PMC) 379-7 listed in the NDA approval letter dated March 20, 2008. The purpose of the PMC was to assess the physico-chemical comparability of TREANDA with common diluents as admixtures to reconstituted TREANDA. This study used lyophilized drug product which had been stored at 25°C for 24 months. The diluents studied were 0.9% sodium

chloride, [redacted], and 2.5% dextrose/0.45% sodium chloride. The tables included in report DD-2008-059 provided data on the levels of the degradation product [redacted](identified in the report as '[redacted]'). This report was not submitted to the NDA in electronic format. FDA provided a letter confirming the fulfillment of the PMC on April 18, 2011.

In response to the e-mail correspondence from the Applicant dated July 3, 2013, the Agency requested that the Applicant "please provide a reference and also include the electronic version of your August 27, 2008 amendment for admixture stability studies to Section 3.2.P.2.6 of the NDA 22249/S-015 resubmission." This e-mail correspondence from ONDQA further states that "the data appears to support the admixture in-use stability to a maximum of 2 hours when stored at room temperature."

The Applicant accepts ONDQA's recommendation and has revised the proposed storage of the admixture solution to 2 hours under room temperature conditions. This resubmission includes an electronic version of Report Number DD-2008-059 per FDA request.

LABELING

The CRL states that "we reserve comment on the proposed labeling until the application is otherwise adequate." In e-mail correspondence from Theresa Carioti, Regulatory Project Manager, Division of Hematology Products, dated June 27, 2013, the Agency proposed modifications to Section 6.3 of the draft prescribing information "as a result of FDA's 915 Safety Report after 10,000 uses of the product." The proposed changes include the addition of pneumocystis jiroveci pneumonia (PJP), pneumonitis, and [redacted]. In e-mail correspondence to Ms. Carioti dated June 28, 2013, the Applicant accepted the addition of PJP and pneumonitis and provided justification for not including [redacted].

The Applicant's request for [redacted] The Applicant accepts DMEPA's recommendation and has revised the labels and labeling accordingly.

REVIEW CYCLE

Per 21 CFR 314.110(b)(1)(iii), "a resubmission of an NDA supplement other than an efficacy supplement constitutes an agreement by the Applicant to start a new review cycle the same length as the initial review cycle for the supplement . . . beginning on the date FDA receives the resubmission." The initial review cycle for this manufacturing supplement was 4 months according to the acknowledgement letter dated April 10, 2013. Considering that the Applicant has accepted the Agency's recommendations and that the majority of the data in the resubmission was previously submitted and reviewed by FDA, the Applicant respectfully requests an action on this supplement soon after receipt of this resubmission.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on July 26, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me. For questions related to CMC, please contact Shirley Speer at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com.

Sincerely,

Michael J. McGraw, PharmD, MS
Director, Regulatory Affairs
Office: 610-727-6136
Cell: (b) (6)
Fax: 610-786-7051
Email: mike.mcgraw@tevapharm.com

From: Martin, Jewell
To: "Mike McGraw"
Cc: Carioti, Theresa
Subject: NDA 22249/S-015 CMC TCON
Date: Tuesday, August 27, 2013 11:29:00 AM

Hello Mike,
We would like to discuss the following issues with you during our TCON scheduled for Wednesday, August 28th at 11AM (EST):
Please provide 12-month primary stability data for the drug product if available. Based on the stability data submitted in the 5/31/13 amendment , a (b) (4) expiration dating period is granted for the drug product when stored at 2° to 8°C (36° to 46°F) in the original package.
This determination is based on ICH Q1A (R2) and ICH Q1E as follows:
ICH Q1A(R2), Section 2.2.7.4 is reproduced below:
Drug products intended for storage in a refrigerator:
If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition.
ICH Q1E, Section 2.5.1.2 is reproduced below:
Drug substances or products intended for storage in a refrigerator:
If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the long-term data. Extrapolation is not considered appropriate.
ICH Q1A(R2), Section 2.2.7.1:
In general, "significant change" for a drug product is defined as:
1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2. Any degradation product's exceeding its acceptance criterion……
The accelerated data show a significant change as described in Section 2.2.7.1 of ICH Q1A(R2). (b) (4)

For example:
180 mg/2 mL Lot 2F003B at 25°C/60%RH Inverted (accelerated condition)

Test	Acceptance Criteria	Initial	1M	3M	6M
(b) (4)					

[redacted] (b) (4)

In addition, the [redacted] (b) (4)

According to ICH Q1A(R2) and ICH Q1E, the proposed shelf life for this drug product should be based on the long-term data. Extrapolation is not considered appropriate. Therefore, a [redacted] (b) (4) shelf life is granted for the drug product when stored at the proposed refrigerated conditions.
Best,

Jewell

Jewell D. Martin, MA, MBA, PMP
Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072
jewell.martin@fda.hhs.gov

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

/s/

JEWELL D MARTIN
08/28/2013

Cephalon

www.cephalon.com

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Phone 610.786.7194
Fax 610.786.7311

August 29, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence 0084
TREANDA® (bendamustine hydrochloride) Injection
RESUBMISSION - CMC Prior Approval Supplement S-015 (b) (4)

AMENDMENT TO COMPLETE RESPONSE – Updated Stability Data

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) Injection, Prior Approval Supplement S-015, submitted on March 8, 2013. This Prior Approval Supplement is to request approval for a new liquid formulation of TREANDA in a single-use vial to replace the currently approved lyophilized product formulation. Reference is also made to the Resubmission for the Complete Response submitted on July 26, 2013, Sequence 0082. Additional reference is made to the e-mail correspondences from Jewell Martin, Regulatory Project Manager, Office of New Drug Quality Assessment (ONDQA), dated August 26 and 27, and the subsequent teleconference between FDA and Teva held on August 28, 2013.

The purpose of this submission is to provide the 12 month primary stability data for drug product registration batches stored at 5°C in the upright and inverted orientations. NDA sections 3.2.P.8.1 and 3.2.P.8.3 are provided along with the updated stability data.

This submission is provided in electronic CTD format (eCTD). The contents of the submission are certified to be virus-free on August 29, 2013 by Teva Branded Pharmaceutical Products R & D, Inc. If there are any technical questions regarding format, validation or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please contact me at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com. For questions not related to CMC, please contact Michael McGraw at (610) 727-6136 or via email at Mike.McGraw@tevapharm.com.

Sincerely,

Shirley Speer
Sr. Manager, Regulatory Affairs, CMC

Branded Pharmaceutical Products R&D

September 5, 2013

Ann Farrell, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-249; Sequence 0085
TREANDA® (bendamustine hydrochloride) Injection
RESUBMISSION - CMC Prior Approval Supplement S-015 (b) (4)
RESPONSE TO FDA REQUEST FOR INFORMATION – Amended Labeling Text
WITHDRAWAL OF (b) (4)

Dear Dr. Farrell:

Reference is made to NDA 22-249 for TREANDA® (bendamustine hydrochloride) Injection, Prior Approval Supplement S-015, submitted on March 8, 2013. This Prior Approval Supplement is to request approval for a new liquid formulation of TREANDA in a single-use vial to replace the currently approved lyophilized product formulation. Reference is also made to the Complete Response Letter (CRL) dated July 2, 2013 and to (b) (4) (b) (4) was found unacceptable.

Further reference is made to the resubmission of supplement S-015 submitted on July 26, 2013, Sequence 0082, and to e-mail correspondence from Theresa Carioti, Regulatory Project Manager, Division of Hematology Products, dated August 26, 2013.

Final reference is made to supplement S-014 submitted April 28, 2013 and to the corresponding approval letter dated August 28, 2013. In this approval letter, the Agency made the following request:

> Also, within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or markedup copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. 610.344.0200 | Fax 610.344.0065 | www.tevapharm-na.com

As requested by Ms. Carioti during a telephone conversation and via e-mail correspondence on August 26, 2013, included with this submission is a marked-up copy of the labeling that shows all relevant changes to the approved labeling for supplement S-014 resulting from the proposed liquid formulation of TREANDA as well as a clean Microsoft Word version.

The Applicant's request for (b) (4) The Applicant accepts DMEPA's recommendation and has revised the labels and labeling accordingly.

Pursuant to 21 CFR §314.65, the Applicant hereby withdraws (b) (4).

Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 2 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 8,Service Pack 1, antivirus engine 9.700.1001,with a release date of September 5, 2013 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact James Mann at 610-727-6133 or via email at James.Mann@tevapharm.com.

If there are any questions concerning this submission, please do not hesitate to contact me. For questions related to CMC, please contact Shirley Speer at (610) 786-7297 or via email at Shirley.Speer@tevapharm.com.

Sincerely,

Michael J. McGraw, PharmD, MS
Director, Regulatory Affairs
Office: 610-727-6136
Cell: (b) (6)
Fax: 610-786-7051
Email: mike.mcgraw@tevapharm.com