CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022249/S-21

Trade Name: **TREANDA**

Generic Name: **Bendamustine Hydrchloride**

Sponsor: **Cephalon, Inc.**

Approval Date: 09/02/2015

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

- Chronic Lymphocytic Leukemia (CLL)
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022249/S-021

SUPPLEMENT APPROVAL

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 August 20, 2015, received August 20, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TREANDA® (bendamustine hydrochloride) Injection (solution) 45mg/0.5mL or 180mg/2mL, and TREANDA® (bendamustine hydrochloride) for Injection (lyophilized powder), 25 mg/vial or 100mg/vial.

This "Prior Approval" supplemental drug application provides for updates to the Unites States Prescribing Information (USPI) with new data regarding the compatibility of devices commonly used in the preparation and administration with Treanda Injection (solution).

APPROVAL & LABELING

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

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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria applies to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

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

ENCLOSURE(S):
Content of Labeling

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
09/02/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 use
TREANDA® (bendamustine hydrochloride) for injection, for intravenous use
Initial U.S. Approval: 2008

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

Dosage and Administration (2)	09/2015
Selection of TREANDA Formulation to Administer (2.1)	09/2015
Preparation for Intravenous Administration (2.4)	09/2015
Admixture Stability (2.5)	03/2015

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

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

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

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

TREANDA is available in two formulations, a solution (TREANDA Injection) and a lyophilized powder (TREANDA for Injection). (2.1)

Do not use TREANDA injection with devices that contain polycarbonate or acrylonitrile-butadiene-styrene (ABS), including most Closed System Transfer Devices (CSTDs). (2.1, 2.4)

For CLL:

- 100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles (2.2)
- Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce dose to 50 mg/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. (2.2)
- 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. (2.2)
- Dose re-escalation may be considered. (2.2)

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 (2.3)
- 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. (2.3)
- Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. (2.3)

General Dosing Considerations:

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

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

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

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

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

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

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

- Myelosuppression: Delay or reduce dose. Restart treatment based on ANC and platelet count recovery. (2.2) Complications of myelosuppression may lead to death. (5.1)
- Infections: Monitor for fever and other signs of infection 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. (6.1)
- Most common hematologic abnormalities for both indications (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. (6.1)

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

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

1.2 Non-Hodgkin Lymphoma (NHL)

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

2 DOSAGE AND ADMINISTRATION

2.1 Selection of TREANDA Formulation to Administer

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

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

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

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

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

If a CSTD or adapter that contains polycarbonate or ABS is used as supplemental protection prior to dilution[1], only use TREANDA for Injection, the lyophilized powder formulation *[see How Supplied/Storage and Handling (16.1)]*.

2.2 Dosing Instructions for CLL

Recommended Dosage:

The recommended dose is 100 mg/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.

2.3 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.

2.4 Preparation for Intravenous Administration

TREANDA is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

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

TREANDA Injection must be diluted in a biosafety cabinet (BSC) or containment isolator.

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

- **If using a syringe to withdraw and transfer TREANDA Injection from the vial into the infusion bag,only use a polypropylene syringe with a metal needle and a polypropylene hub to withdraw and transfer TREANDA Injection into the infusion bag.**

- Each vial of TREANDA Injection is intended for single dose only.

- Aseptically withdraw the volume needed for the required dose from the 90 mg/mL solution using a polypropylene syringe with a metal needle and a polypropylene hub.

- Immediately transfer the solution to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 – 0.7 mg/mL.

- **After dilution of TREANDA Injection into the infusion bag, devices that contain polycarbonate or ABS, including infusion sets, may be used.**

- Visually inspect the filled syringe and the prepared infusion bag to ensure the lack of visible particulate matter prior to administration. The admixture should be a clear colorless to yellow solution.

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

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

If a closed system transfer device or adapter that contains polycarbonate or ABS is to be used as supplemental protection during preparation[1], only use TREANDA for Injection, the lyophilized formulation.

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

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

General Information

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

2.5 Admixture Stability

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

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

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

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

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored under refrigerated conditions at 2°-8°C (36-47°F) or for

3 hours when stored at room temperature (15-30°C or 59-86°F) and room light**.** Administration of reconstituted and diluted TREANDA for Injection must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

- TREANDA Injection: 45 mg/0.5 mL or 180 mg/2 mL in a single-dose vial.
- TREANDA for Injection: 25 mg or 100 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

TREANDA caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be $\geq 1 \times 10^9$/L and the platelet count should be $\geq 75 \times 10^9$/L. *[see Dosage and Administration (2. 2) and (2. 3)]*

5.2 Infections

Infection, including pneumonia, sepsis, septic shock, 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)]*

6.1 Clinical Trials Experience

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

Chronic Lymphocytic Leukemia

The data described below reflect exposure to TREANDA in 153 patients with CLL studied in an active-controlled, randomized trial. The population was 45-77 years of age, 63% male, 100% white, and were treatment naïve. All patients started the study at a dose of 100 mg/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.

Non-Hodgkin Lymphoma

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TREANDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: 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/m^2 (70 mg/kg) in mice administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (exencephaly, cleft palates, accessory rib, and spinal deformities) and decreased fetal body weights. This dose did not appear to be maternally toxic and lower doses were not evaluated. Repeat intraperitoneal dosing in mice on gestation days 7-11 resulted in an increase in resorptions from 75 mg/m^2 (25 mg/kg) and an increase in abnormalities from 112.5 mg/m^2 (37.5 mg/kg) similar to those seen after a single intraperitoneal administration. Single intraperitoneal doses of bendamustine from 120 mg/m^2 (20 mg/kg) in rats administered on gestation days 4, 7, 9, 11, or 13 caused embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in external [effect on tail, head, and herniation of external organs (exomphalos)] and internal (hydronephrosis and hydrocephalus) malformations were seen in dosed rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The 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

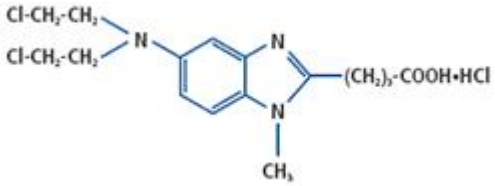
The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

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

TREANDA 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 a single-dose vial 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.

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

TREANDA (bendamustine HCL) for Injection is intended for intravenous infusion only after reconstitution with Sterile Water for Injection, USP, and after further dilution with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. It is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single-dose vial. Each 25-mg vial contains 25 mg of bendamustine hydrochloride and 42.5 mg of mannitol, USP. Each 100-mg vial contains 100 mg of bendamustine hydrochloride and 170 mg of mannitol, USP. The pH of the reconstituted solution is 2.5 - 3.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 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 65.7x10^9/L vs. 65.1x10^9/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either TREANDA at 100 mg/m^2, administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL[1].

The results of this open-label randomized study demonstrated a higher rate of overall response and a longer progression-free survival for TREANDA compared to chlorambucil (see Table 5). Survival data are not mature.

Table 5: Efficacy Data for CLL

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

CI = confidence interval

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

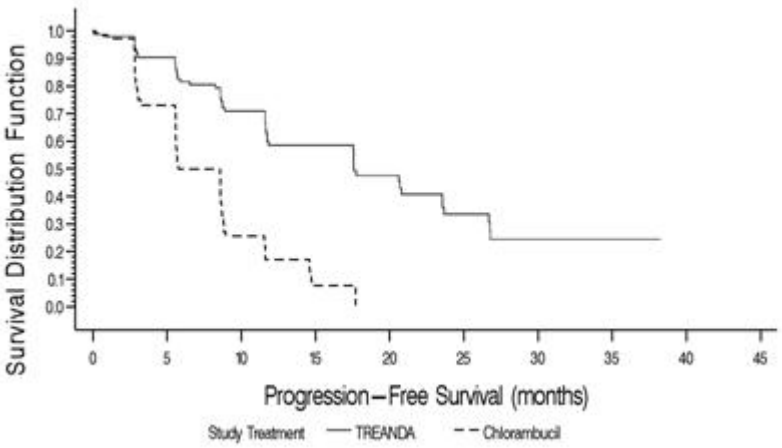
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

† PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, hemoglobin >110g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

†† PFS was defined as time from randomization to progression or death from any cause.

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

Figure 1. Progression-Free Survival



14.2 Non-Hodgkin 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 July 21, 2015, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

TREANDA is a cytotoxic drug. Follow applicable special handling and disposal procedures[1]. Care should be exercised in the handling and preparation of solutions prepared from TREANDA Injection and TREANDA for Injection. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If gloves come in contact with TREANDA Injection prior to dilution, remove gloves and follow disposal procedures[1]. 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.

16.2 How Supplied

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

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

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

- NDC 63459-390-08: 25 mg white to off-white lyophilized powder in a 8 mL amber single-dose vial
- NDC 63459-391-20: 100 mg white to off-white lyophilized powder in a 20 mL amber single-dose vial

16.3 Storage

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

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.

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

TREANDA for Injection may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) (see USP Controlled Room Temperature). Retain in original package until time of use to protect from light.

17 PATIENT COUNSELING INFORMATION

Allergic (Hypersensitivity) Reactions

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

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-011

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022249/S-21

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

NDA Supplement Number: Teva submitted information on the compatibility of Treanda Injection with various devices in a number of supplements. In order to have a comprehensive overview, the review of all the submissions related to Teva's compatibility studies have been consolidated in this review. Included below are the supplements that Teva submitted compatibility information. For a complete list of the submissions reviewed, refer to the table in item #1 of this review.

1. NDA 22249/S-015 - New liquid formulation of Treanda, Treanda injection
2. NDA 22249/S-019 (Labeling Supplement – Data supporting the use of closed system transfer devices, vial adapters, polypropylene syringes, disposable gloves and IV administration sets) .
3. NDA 22249/S-021 – Labeling supplement. Communication of device compatibility, Dear Healthcare Provider Letter, and Proposal for Maintaining the List of Compatible Devices

Tracked Safety Issue (TSI) # 1368: TSI #1368 has been satisfactorily addressed from a CMC standpoint.

Final CMC Recommendation: Approval

Executive Summary

NDA 22249/S-021 is a labeling supplement that provides for the revision of the prescribing information for Treanda in order to communicate new information about the compatibility of Treanda injection with devices that are commonly used in the preparation and administration of Treanda. This supplement includes labeling for the communication of device compatibility, Dear Healthcare Provider Letter, and a Proposal for Maintaining the List of Compatible Devices. The results of these studies are evaluated and summarized in this review.

Summarized in the tables 1-5 are a list of compatible/incompatible devices for use with Treanda injection. The bendamustine HCl in the Treanda drug product can cause interference with currently available analytical methods used to detect leachable substances. Because of the interference of bendamustine, testing for leachables with the active drug product present in the samples make it difficult to distinguish between solutes in the product and potential leachables. To eliminate the potential for interference, the compatibility work was conducted with the placebo containing N,N-dimethylacetamide (DMA) (66% v/v) and propylene glycol (34% v/v).

Summary of compatible devices

1. IV Administration Sets: The compatibility of a variety of IV administration sets with placebo diluted with 0.9% saline IV solution was tested by visual examination, organic impurities by LC-MS and GC-MS testing. Based on the results of these studies, the IV administration sets listed in Table 1 may be used with diluted Treanda injection.

Table 1: Compatibility of IV Administration Sets with Treanda injection

Manufacturer/ supplier	Device	Compatibility
B. Braun REF NF3482	Safeline IV Administration set with universal spike, safeline injection site, and spin –lock connector	Compatible
B. Braun REF V1921	Secondary IV set with Universal spike and Spin-lock connector	Compatible
Baxter REF 2C7575	Solution with Duo Vent Spike – Not recommended for gravity infusion	Compatible
Baxter REF 2H8480	Clear Link System- Non-DEHP solution set with Duo-Vent Spike	Compatible
Becton Dickinson REF 515301	BD Phaseal Secondary Set (C60)	Compatible
ICU Medical REF CH3011	Admin Set w/20 drop integrated Clave® Drip chamber, spiros®, Hanger	Compatible

2. Syringes and Corresponding Needles: Samples of placebo stored in the polypropylene syringes with attached needles for 120 minutes were tested for Appearance, Organic impurities by LC-MS, and Organic impurities by GC-MS.

   In addition, samples of placebo held in the polypropylene syringes for 120 minutes and then transferred to IV bags were tested for particulate matter, USP <788>. Based on these studies, the polypropylene syringes listed in Table 2 with metal needles can be used to transfer Treanda injection from the vial to the IV bags. The applicant has also proposed the use of the 3 mL syringes for the manufacturer's listed in table 2. Since the material of construction is the same for the 3 mL and 5 mL syringe, both are acceptable for use with Treanda injection.

Table 2: Syringes and Corresponding Needles from Six Manufacturers

Manufacturer	Device	Ref #	Material of Construction	Comments
Becton Dickinson (BD)	5 mL syringe 18 G 1" needle	309646 305195	Polypropylene, thermoelastomer plunger,	Compatible
Covidien Monoject	5 mL syringe 18 G 1" needle	1180600777 1188818100	Polypropylene, thermoelastomer plunger	Compatible
B. Braun	5 mL syringe 18 G 1" needle	4617053V-02 4650018-02	Polypropylene, thermoelastomer plunger	Compatible

Manufacturer	Device	Ref #	Material of Construction	Comments
Air-Tite Norm Ject	5 mL syringe 18 G 1" needle	4K06048 8300012773	Polypropylene, thermoelastomer plunger	Compatible
Medline	5 mL syringe 18 G 1" needle	SYR105010 SYRS100185	Polypropylene, thermoelastomer plunger	Compatible
Terumo	5 mL syringe 18 G 1" needle	SS-05L SG3-1825	Polypropylene, thermoelastomer plunger	Compatible

3. Compatibility of Different Glove Brands: The qualitative compatibility was determined by application of placebo solution to the glove surface for 10 minutes followed by a visual evaluation of any solution breakthrough or evidence of deformation. All gloves that passed the initial qualitative screening were evaluated for permeability. The permeability evaluation consisted of measuring the presence or absence of bendamustine by HPLC after exposure of each glove material to Treanda injection for 10 minutes. Based on the results of the qualitative screening and the permeability evaluation the brands of gloves are acceptable for use with Treanda injection is shown in the first 8 rows in table 3.

Table 3: Compatibility of Different Glove Brands with Treanda injection

Trademark name	Manufacturer	Materials	Comments
ChemoPlus	Covidien	Latex	Compatible
EP-Blue	Innovative Healthcare Corporation	Latex	Compatible
Jackson Safety G29	Kimberly Clarke	Neoprene	Compatible
NeoPro	Microflex	Chloroprene	Compatible
NitriDerm	Innovative Healthcare Corporation	Nitrile	Compatible
Purple	Halyard	Nitrile	Compatible
Purple KC 500	Kimberly Clarke	Nitrile	Compatible
UltraSense EC	Microflex	Nitrile	Compatible
ChemoPlus	Covidien	Nitrile	Not compatible
NeoGuard	Microflex	Chloroprene	Not compatible
SafeGrip	Microflex	Latex	Not compatible
Supreno EC	Microflex	Nitrile	Not compatible
Ultra One	Microflex	Latex	Not compatible

4. Closed System Transfer Devices (CSTD): CSTD compatibility studies using placebo was tested by visual examination, organic impurities by LC-MS, GC-and particulate matter. Results demonstrate that only the BD Phaseal CSTD was found to be compatible with Treanda injection (see table 4).

Table 4: Compatibility of CSTDs for Use with Treanda injection

CSTD	**Use with Treanda injection**
Becton Dickenson (BD) Phaseal consists of: Protectors P14 – REF 515100 Injector Luer Lock N35 REF 515003 Infusion Adapter C100 REF 515306 BD PP Syringe – REF 309646 and 309657	Compatible
Teva Tevadaptor	Not compatible
ICU Medical	Not compatible
Carefusion	Not compatible
Equashield	Not compatible

5. Vial Adapters: Vial adapter compatibility studies using placebo was tested by visual examination, organic impurities by LC-MS, GC-MS, and particulate matter. Results demonstrate that the vial adapters listed as compatible in table 5 can be used with Treanda injection.

Table 5: Vial Adapter Compatibility with Treanda injection

Vial adapter	**Use with Treanda injection**
Baxter CHEMO- AIDE	Compatible
Medimop	Compatible
Alaris Products 2202E	Compatible
Alaris Products 2203E	Compatible
Baxter Interlink	Incompatible
B Braun	Incompatible
CareFusion	Incompatible
MedStream	Incompatible

1. Submission(s) Being Reviewed:

Submission submitted under	Submission Date	Submission eCTD#/ SDN	Comments
SUPPL-15	03/04/2015	109/429	Compatibility data of TREANDA concentrate solution with polypropylene syringes
SUPPL-19	3/06/2015	110(430)	New Labeling Supplement
SUPPL-19	3/09/2015	111(431)	Response to FDA Request for Information – Tracked Changes version of Prescribing Information and Revised Dear Healthcare Provider Letter
SUPPL-19	3/10/2015	112(432)	Response to FDA Request for Information – Final Dear Healthcare Provider Letter, Final Revisions to Prescribing Information and CMC Compatibility Data
SUPPL-19	3/13/2015	113(433)	Response to FDA Information Request Compatibility of Diluted Treanda injection. Data demonstrating the compatibility of diluted Treanda injection with infusion tubing, spikes, and any accessories in the fluid path during the administration of the drug.
General Corresp.	03/18/2015	114/435	Teva submitted the following: 1. Updated timeline for Teva's Communication Plan. 2. Number of complaints and inquiries since the DHCP letter was posted to the website. 3. Comprehensive list of the proposed CMC compatibility studies.
SUPPL-19	3/23/2015	115(436)	Response to FDA Information Request - Compatibility of IV Infusion Sets with Treanda liquid – ABS spikes and PC syringes
SUPPL-19	3/26/2015	116(437)	Response to FDA Information Request – Resubmit: Compatibility of IV Infusion Sets with Treanda liquid – ABS spikes and PC syringes
SUPPL-19	3/27/2015	117(438)	Response to FDA Information Request – Complaints and Inquiries
SUPPL-19	4/01/2015	118(439)	Response to FDA Information Request – Resubmit: Compatibility of IV Infusion Sets with Treanda liquid – ABS spikes and PC syringes – CORRECTION. Teva said that they discovered that the solutions in their previous compatibility studies submitted on 3/23 and 3/26 for spikes and syringes were prepared incorrectly. They repeated the studies using the desired concentration of 0.3%. The results of the new study did not demonstrate any differences from the previously reported results.
SUPPL-19	4/16/2015	119(440)	Response to FDA Information Request – Compatibility of IV Infusion Sets with Treanda liquid – Material of construction other than ABS and PC / PC syringes from various vendors. (1) Compatibility of IV administration sets with Treanda liquid in the 0.9% saline infusion solution. (2) Compatibility of polypropylene syringes from various

			vendors with Treanda liquid.
SUPPL-19	6/01/2015	126(457)	Response to FDA Information Request – Compatibility of commonly used gloves with Treanda liquid
SUPPL-19	6/04/2015	127(459)	Response to FDA Information Request – Compatibility of commonly available closed system transfer devices with Treanda liquid
SUPPL-19	7/09/2015	132(471)	Response to FDA Information Request Compatibility Study – Polypropylene syringes from various vendors
SUPPL-15	7/10/2015	133(472)	Response to FDA Information Request – Compatibility of commonly available vial adaptors with Treanda liquid
SUPPL-15	7/14/2015	134(473)	Response to FDA Information Request Compatibility Study – Polypropylene syringes from various vendors
SUPPL-021	8/20/2015	136(477)	New Labeling Supplement

3. **Proposed Changes -** NDA 22249/S-015 and S-019: Data supporting the use of closed system transfer devices, vial adapters, polypropylene syringes, disposable gloves, and IV administration sets) .
   NDA 22249/S-021 – Labeling supplement. Communication of device compatibility, Dear Healthcare Provider Letter, and Proposal for Maintaining the List of Compatible Device

4. **Clinical Review Division**: Division of Hematology Products (DHP)

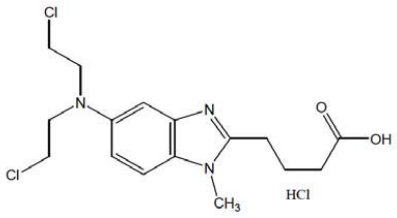
5. **Name and Address of Applicant**:

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

6. **Drug Product**:

Drug Name	**Dosage Form**	**Strength**	**Route of Administration**	**Rx or OTC**	**Special Product**
Treanda (bendamustine hydrochloride) Injection	Injection	45 mg/0.5 mL 180 mg/2 mL	Intravenous	Rx	No

7. **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: C16H21Cl2N3O2 • HCl MW: 394.72

8. **Indication**: 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.
   - Indolent B - cell non - Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab - containing regimen.

9. **Supporting/Relating Documents**: None

10. **Consults**: None

11. **Conclusions & Recommendations**:

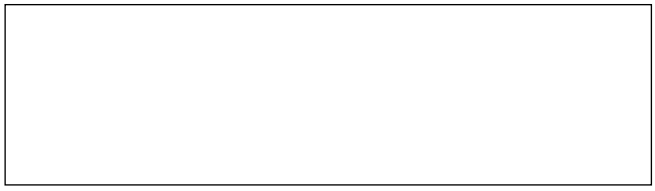
    Approval

12. **Comments/Deficiencies to be conveyed to Applicant**: None

13. **Primary Reviewer**:
    Janice Brown, MS, QAL, Branch 2, Division of New Drug Products I, Office of New Drug Products, Office of Pharmaceutical Quality (OPQ)

    Ilan Geerlof-Vidavsky, Ph.D., Chemist, Division of Pharmaceutical Analysis, Office of Testing and Research, Office of Pharmaceutical Quality (OPQ)

14. Secondary Reviewer:
Hasmukh Patel, Ph.D., Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ



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CMC Assessment

Background: NDA 22249/S-021 – Labeling supplement. This supplement includes labeling for the communication of device compatibility, Dear Healthcare Provider Letter, and Proposal for Maintaining the List of Compatible Devices based on the studies performed in S-019.

NDA 22249/S-019 is a "Changes Being Effected" supplement that provides for updates to the PI for Treanda Injection (solution) and Treanda for Injection (lyophilized powder). The labeling revisions include information on the incompatibility of Treanda Injection with Closed System Transfer Devices (CSTD) made of polycarbonate or acrylonitrile-butadienestyrene (ABS). This supplement was approved on 3/10/2015. Information on the compatibility of devices with Treanda injection was submitted under S-019 and S-015 (supplement for a new dosage form, Treanda injection).

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution) is not compatible with CSTDs, adaptors, and syringes containing polycarbonate or ABS. This incompatibility leads to device failure, possible product contamination, and potential serious adverse health consequences to the practitioner or to the patient if they receive product contaminated with dissolved ABS or polycarbonate. Treanda injection (45 mg/0.5 mL or 180 mg/2 mL solution) contains N,N-dimethylacetamide (DMA) which is incompatible with polycarbonate and ABS. CSTDs, adaptors, and syringes containing polycarbonate or ABS dissolve when contacting DMA.

The Treanda injection formulation (Treanda Injection) was submitted as S-015 and approved on 9/13/2013. The composition of the Treanda injection liquid formulation is reproduced in Table 1.

Table 1: Composition of the 45 mg/0.5 mL and 180 mg/2.0 mL Treanda injection

Component	Function	Unit	
		45 mg/0.5 mL	180 mg/2.0 mL
Bendamustine HCl	(b) (4)	45 mg	180 mg
Propylene Glycol, USP		0.16 mL	0.62 mL
N,N-Dimethylacetamide, EP		0.31 mL	1.24 mL
Total		0.5 mL	2.0 mL

- **Submission dated 3/04/2015, eCTD#109/ SDN#429**

On 3-2-2015, a teleconference was held between Teva and FDA discussing the incompatibility of the Treanda injection with Close System Transfer Devices (CSTD), adaptors or syringes containing acrylonitrile-butadienestyrene (ABS) or polycarbonate. During this teleconference, the Agency requested that Teva submit new compatibility data of Treanda injection with polypropylene syringes.

FDA Request: Provide data to support the compatibility of BD polypropylene syringes with the Treanda injection product.

Teva's Response: The initial determination of suitability of BD polypropylene (PP) syringes (Becton Dickinson, Franklin Lakes, NJ, USA;) was demonstrated during in-use studies performed for Treanda injection product during development. Additional studies were performed to determine the compatibility of BD polypropylene 5 mL syringes with metal needles with Treanda injection. Compatibility was evaluated by the following tests: appearance, organic impurities, and particulate matter.

A 5 mL sample of Treanda drug product or placebo was filled into 5 mL polypropylene syringes. Particulate matter, USP<788> testing was also performed by transferring Treanda injection by polypropylene syringe to IV bags containing 0.9% sodium chloride solution (500 mL bag) or 2.5% dextrose/0.45% sodium chloride solution (1000 mL bag) at the high dose (0.7 mg/mL).

Results

Appearance - All appearance results for either Treanda drug product or placebo stored in the polypropylene syringes for up to 120 minutes demonstrated no cloudiness or visible particles.

Organic Impurities by Liquid Chromatography-Mass Spectrometry (LC-MS) - A comparison of the total ion chromatograms (TIC) of the placebo control versus the placebo sample that was stored in polypropylene syringes for 120 minutes showed one significant minor peak. An unknown compound with a retention time of 10.92 minutes and mass of 501 was detected in the 120 minute placebo test that was absent in the placebo control. However, the signal for this unknown was less than that which was observed for a 0.1 ppm reserpine external standard. According to Teva, at <0.1 ppm, this unknown compound does not represent a safety concern, and supports the continued use of BD polypropylene syringes.

Organic Impurities by Gas Chromatography-Mass Spectrometry (GC-MS) - GC-MS analysis of volatile and semi-volatile analytes in placebo stored in polypropylene syringes for 120 minutes yield no peaks observed that were not in the control.

Particulate matter, USP <788> - Particulate matter testing was performed at each required time point in 3 bags for each diluent (n=3). The results demonstrate that no solubilized extracts from the polypropylene syringes have precipitated in the infusion bags.

In-use Studies for Treanda liquid - As part of Treanda liquid development, in-use studies were conducted to demonstrate the stability of the Treanda liquid formulation when diluted to 500 mL in IV bags containing 0.9% sodium chloride solution or 2.5% dextrose/0.45% sodium chloride solution. These data were summarized in NDA 22-249. The HPLC data showed that only impurities or degradants from bendamustine HCl active ingredient were observed. No additional leachables from the polypropylene syringes were detected. Particulate matter testing produced acceptable results. These studies further support the compatibility of the Treanda liquid formulation with polypropylene syringes.

Particulate Matter - In addition to the chemical stability of drug product in intravenous infusion bags, diluted solutions of drug product in 500 mL each of 0.9% Sodium Chloride Injection, USP and 2.5% Dextrose/0.45% Sodium Chloride Injection, USP at 0.2 mg/mL and 0.7 mg/mL concentrations were subjected to particulate matter testing as described in United States Pharmacopeia, General Chapter Particulate Matter Testing in Injections <788> after

preparation. The diluted solutions were colorless and free from particulate matter (with no change in particulate matter) under the conditions utilized for the study.

Evaluation: Satisfactory.

1. **BD Polypropylene syringe results after exposure to Treanda injection**

   - **Organic Impurities by Liquid Chromatography-Mass Spectrometry (LC-MS) - A comparison of the total ion chromatograms (TIC) of the placebo control versus the placebo sample that was stored in polypropylene syringes for 120 minutes showed one significant additional peak and several minor peaks. An unknown compound with a retention time of 10.92 minutes and mass of 501 was detected in the 120 minute placebo that was absent in the placebo control at a level of <0.1 ppm.** ***According to the nonclinical reviewer, a level of 0.1 ppm in a product of 50 mg/m2 leads to an exposure of approximately 10 ng/d of this unknown compound. The level of this unknown compound was found acceptable by the nonclinical review team (see review by John Leighton, Ph.D. on 3/10/15).***

   - **Appearance - Results of appearance by visual examination of the polypropylene syringes after storing Treanda drug product or placebo in the syringe for 120 minutes show no cloudiness or visible particles in the solution or a change from the T_0 or the control.**

   - **Organic Impurities by Gas Chromatography-Mass Spectrometry (GC-MS) - No significant differences were noted between the control samples and placebo samples stored in the BD polypropylene syringes for 120 minutes.**

2. **Stability of the Treanda admixture – Teva resubmitted the in-use studies from NDA 22249 for Treanda injection diluted into 500 mL of 0.9% Sodium Chloride Injection, USP or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP at 0.2 mg/mL and 0.7 mg/mL concentrations and evaluated for chemical stability. After a response to a CR letter, Dr. Lin found the results acceptable provided that the admixture is stored for 24 hours 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.**

3. **Samples of Treanda injection stored in the BD polypropylene syringes for up to 120 minutes and then transferred to IV bags passed the USP <788> particulate matter testing.**

- **Submission dated 3/06/2015, eCTD#110/ SDN#430, 3/09/2015, eCTD#111/ SDN#431, and 3/10/2015, eCTD#112/ SDN#432:**

  Refer to the labeling supplement (S-019) approved on March 10, 2015 that include updates to the Unites States Prescribing Information (USPI) for both formulations, Treanda injection (Solution) and Treanda for Injection (lyophilized powder). In addition, the label provides for additional information on the use of Treanda liquid formulation and

incompatibilities with Closed System Transfer Devices (CSTD) that contains polycarbonate or acrylonitrile-butadienestyrene (ABS).

- **Submission dated 3/13/2015, eCTD#113/ SDN#433**

In an e-mail dated March 13, 2015, Kimberly Scott, Regulatory Project Manager, requested the following CM information:

FDA question: Please provide data to demonstrate the compatibility of diluted Treanda injection with infusion tubing, spikes, and any accessories in the fluid path during the administration of the drug. Include in your study items containing acrylonitrile-butadiene-styrene (ABS) or polycarbonate. This study should cover the in-use period of the infusion solution to patients.

Teva's Response:
Each vial of Treanda liquid contains 180 mg or 45 mg (90 mg/mL) of bendamustine HCl, the active ingredient. Bendamustine HCl is dissolved in N,N-dimethylacetamide (DMA) 66% vol/vol and Propylene Glycol, 34% vol/vol.

After the appropriate amount of Treanda liquid is aseptically transferred to a 500 mL infusion bag, DMA is diluted and its concentration is not more than 0.3% at the high dose. The calculation for determining the DMA concentration in the infusion bag for the high dose is presented:

Dosage: 90 mg/kg day
For calculation purposes, 120 mg/m2 (as highest dose) is used
DMA concentration in infusion bag and amount administered/patient/infusion
120 mg/m2 x 1.8 m2 = 216 mg/90 mg/mL = 2.4 mL x 0.66 = 1.6 mL per dose
1.6 mL / 500 mL x 100% per treatment = 0.3%
The amount of DMA in the infusion bag after dilution with saline = 0.3%

The recommended infusion time is up to 1 hour. At this concentration and short exposure time, DMA is not expected to have any incompatibility with infusion tubing, spikes, and any accessories in the fluid path during the administration of the drug. Data generated during in-use studies demonstrating the compatibility of Treanda liquid with PVC and non-PVC (polyolefin, polyethylene (PE)) 500 mL infusion bags were submitted in NDA 022249 and in a communication to the FDA on 04-Mar-2015. In these in-use studies, no incompatibility with the infusion bags studied was noted.

Evaluation: Not satisfactory The applicant explained that the in-use studies were submitted to the FDA on 3/4/2015; however, the information submitted to the NDA did not include the types of infusion tubing, spikes and accessories. The information was requested again and reviewed in submission dated 4/1/2015 and 4/16/15 in this review.

- **Submission dated 3/18/2015, eCTD#114/ SDN#435**

Teva submitted the following information:
1. Updated timeline for Teva's Communication Plan.
2. Number of complaints and inquiries since the DHCP letter was posted to the website.

3. Comprehensive list of the proposed CMC compatibility studies.

Evaluation: Satisfactory.

The CMC team agreed to the proposed timelines for the completion of the CMC compatibility studies.

- **Submission dated 3/23/2015, eCTD#115/ SDN#436**

In an e-mail dated March 13, 2015, Kimberly Scott, Regulatory Project Manager, requested the following CMC information:

Please provide data to demonstrate the compatibility of diluted Treanda injection with infusion tubing, spikes, and any accessories in the fluid path during the administration of the drug. Include in your study items containing acrylonitrile-butadiene-styrene (ABS) or polycarbonate. This study should cover the in-use period of the infusion solution to patients.

Teva's response: After conducting and reporting the studies performed to evaluate the compatibility of ABS and polycarbonate (PC) with Treanda liquid in 0.9% saline, Teva discovered that the "Placebo Sample Solution" described in the study design section was prepared incorrectly. The results of this study were reported on March 23, 2015 (Seq 0115) and March 26, 2015 (Seq 0116). In that study, 1.6 mL of Treanda placebo was transferred to a 500 mL 0.9% saline infusion bag instead of the required 2.4 mL. This resulted in a DMA concentration of 0.2% instead of the desired concentration of 0.3%. Because of this error, the study has been repeated with the correct DMA concentration of 0.3%. The data did not demonstrate any differences from the previously reported results. The results of the new study are provided in the 4/1/15 submission.

Evaluation: See 4/1/2015 Submission review.

Submission dated 3/26/2015, eCTD#116/SDN#437
The study in this submission was repeated and submitted in the 4/1/15 submission due to incorrect preparation of the Placebo Sample Solution preparation. Refer to the 4/1/15 submission review.

Submission dated 3/27/2015, eCTD#117/SDN#438

The Division's original question from an e-mail dated March 25, 2015 is presented below in bold, followed by the sponsor's response.

FDA QUESTION:
Has Teva received any additional inquiries or complaints since our last meeting, March 16, 2015?

Teva's Response: Below is a summary of the complaints and inquiries received for Treanda liquid for the time period of 3/16/2015 through 3/25/2015:

- 203 total contacts were received between 3/16/2015 – 3/25/2015

    - These contacts were received by either: Quality for Complaints, by Medical Affairs for medical inquiries, and/or by Pharmacovigilance for Adverse Events
        i. 155 contacts were for product compatibility related inquiries (and/or no defect complaints)
        ii. 27 contacts were for availability of the product (especially for the availability of the lyophilized product)
        iii. 15 contacts were related to storage (and possible temperature excursions)
        iv. 10 contacts were logged as use of Treanda liquid with a CSTD (with no AEs reported)
        v. 1 contact was for miscellaneous information

Please note that the contacts above represent a total of 208 reasons. This is due to some contacts resulting in requests for multiple types of information. For example, a contact could 1.) ask about the availability of the lyophilized product and 2.) ask about the compatibility of the product with a CSTD component

Evaluation: Information noted.

Submission dated 4/1/2015, eCTD#118/SDN#439 - Response to FDA Information Request – Resubmit: Compatibility of IV Infusion Sets with Treanda liquid – ABS spikes and PC syringes - CORRECTION

This submission provides for a correction of the compatibility studies of Treanda placebo with ABS spikes and PC syringes. Teva explained that they discovered that the solutions in their previous compatibility studies submitted on 3/23 and 3/26 for spikes and syringes were prepared incorrectly. They repeated the studies using the desired concentration of 0.3%. The results of the new study did not demonstrate any differences from the previously reported results.

In an e-mail dated March 13, 2015, and March 25, 2015, Kimberly Scott, Regulatory Project Manager, requested the following information:

FDA questions:

1. **Please provide data to demonstrate the compatibility of diluted Treanda injection with infusion tubing, spikes, and any accessories in the fluid path during the administration of the drug. Include in your study items containing acrylonitrile-butadiene-styrene (ABS) or polycarbonate.**

   This study should cover the in-use period of the infusion solution to patients.

2. **We have also reviewed the additional CMC data that was submitted to us on Monday, March 23rd. We have the following additional clarification. Please**

provide a response to the below information request by 5PM today. In the interest of time, please send via email and then follow-up with an official submission.

The compatibility data that were submitted on 3/23/15 show new peaks in chromatograms that may be due to leachables. Please explain what the following peaks are:
Figure 1: Peaks at 4.79 and 12.37
Figure 3: Peaks at 5.36, 7.20, 7.57, 9.84 (these peaks also show in the saline control –
syringe in saline for 3 hours) and 10.59
Figure 4: The region between 1.70 and 3.76 appears different between placebo test and placebo blank.

Teva's response: Each vial of Treanda liquid contains 180 mg or 45 mg (90 mg/mL) of bendamustine HCl, the active ingredient. Bendamustine HCl is dissolved in N,N-dimethylacetamide (DMA) 66% vol/vol and propylene glycol, 34% vol/vol. After the appropriate amount of Treanda liquid is aseptically transferred to a 500 mL infusion bag, DMA is diluted and its concentration is not more than 0.3% at the high dose. The calculation for determining the DMA concentration in the infusion bag for the high dose was included in the submission.

Studies were performed to determine the component compatibility using the placebo of the drug product diluted with 0.9% saline to the concentration representative of the high dose. Acrylonitrile-butadiene-styrene (ABS) spikes and polycarbonate (PC) syringes were used to determine the compatibility of the Treanda placebo infusion solution with these materials commonly found in IV infusion sets. Compatibility was determined by testing appearance and organic impurities.

The following were tested:

- 500 mL 0.9% Sodium Chloride IV bag Baxter Viaflo Ref FE1323 lot# 14K07E5M expiration date: 10/2016
- Acrylonitrile-butadiene-styrene (ABS) Spike from B Braun adset (PVC w/ DEHP) Ref# NF3482 lot# 0061160916 expiration date : 5/2016
- Polycarbonate (PC) syringe - 1 mL, BD ref 309628 lot# 9197985
- Disposable needle - 18 G 1", BD ref 305195 lot# 3117465

Acrylonitrile-butadiene-styrene (ABS) Spikes
Placebo Test Samples:
Three 20 mL beakers were filled with ~ 18 mL each of the Placebo Sample Solution from the infusion bag and the ABS spike portion of adsets were placed into the solution and covered with
foil. The ABS spikes were left in the solution at ambient room temperature for 3 hours.
Saline Control Samples:
Three 20 mL beakers were filled with ~ 18 mL each of 0.9% Saline Control Solution and the ABS spike portion of adsets were placed into the solution and covered with foil. The ABS spikes were left in the control solution at ambient room temperature for 3 hours.
Saline Blank Samples:

Saline blanks were prepared by filling the Saline Control Solution that was not exposed to ABS or PC directly into HPLC vials.

Placebo Blank Samples:

Placebo blanks were prepared by filling the Placebo Sample Solution that was not exposed to ABS or PC directly into HPLC vials.

Polycarbonate (PC) syringes

Placebo Test Samples:

Three 1 mL PC syringes were filled with the Placebo Sample Solution from the infusion bag. The filled PC syringes were left at ambient room temperature for 3 hours.

Saline Control Samples:

Three 1 mL PC syringes were filled with the 0.9% Saline Control Solution. The filled PC syringes were left at ambient room temperature for 3 hours.

Saline Blank Samples:

Saline blanks were prepared by filling the Saline Control Solution that was not exposed to ABS or PC directly into HPLC vials.

Placebo Blank Samples:

Placebo blanks were prepared by filling the Placebo Sample Solution that was not exposed to ABS or PC directly into HPLC vials.

All samples were tested according to the protocol presented in Table 1.

Table 1: Compatibility Testing Protocol

	ABS Spike		PC Syringe	
	Initial	**3 Hours**	**Initial**	**3 Hours**
Saline blank solution	X	NA	X	NA
Placebo blank solution	X	NA	X	NA
Saline control solution	X	XY	X	XY
Placebo test solution	X	XY	X	XY

X = Appearance
Y = Organic impurities
NA = Not applicable n = 3

Results

ABS Spike Compatibility Study - Using the placebo of the drug product diluted with 0.9% saline to the concentration representative of the high dose.

- **Appearance -** All appearance results for the ABS spike test solutions demonstrated no cloudiness or visible particles.
- **Organic Impurities by Liquid Chromatography-Mass Spectrometry (LC-MS) -** A comparison of the total ion chromatograms (TIC) of the saline and placebo blanks, the saline control sample, and the placebo test sample of the ABS spikes after 3 hours showed no new peaks. Representative chromatograms illustrate that no additional peaks were observed.

- **Organic Impurities by Gas Chromatography-Mass Spectrometry (GC-MS) -** GC-MS analysis of volatile and semi-volatile analytes in the saline and placebo blanks, the saline control sample, and the placebo test sample of the ABS spike solutions after 3 hours yielded no peaks observed that were not in the control. Representative chromatograms illustrates that no additional peaks were observed.

PC Syringe Compatibility Study - Using the placebo of the drug product diluted with 0.9% saline to the concentration representative of the high dose.

- **Appearance -** All appearance results for the PC syringe test solutions demonstrated no cloudiness or visible particles.

- **Organic Impurities by Liquid Chromatography-Mass Spectrometry (LC-MS) -** A comparison of the total ion chromatograms (TIC) of the saline and placebo blanks, the saline control sample, and the placebo test sample that were stored in polycarbonate (PC) syringes for 3 hours showed no new peaks. Representative chromatograms illustrate that no additional peaks were observed.

Evaluation: Not Satisfactory. Results of organic impurities detected by LC-MS and GC-MS testing of the placebo (containing excipients N,N-dimethylacetamide (DMA) 66% vol/vol and propylene glycol, 34% vol/vol.) diluted in 500 mL 0.9% saline and exposed to ABS spikes (see figures 1 - LC-MS and 3 GC-MS) and PC syringe show multiple unidentified peaks. No peak integration was performed so no quantitative estimate of individual and total amount of leachables was included in the submission. Results of visual examination were acceptable and did not exhibit any cloudiness or visible particulates.

Regarding the IR for the compatibility data submitted on 3/23/15. According to Teva, no new peaks were observed in this repeat testing; therefore, no response to this IR was provided.

IR to the applicant:
We do not agree with your conclusion that the GC-MS analysis of the placebo infusion solution held in the PC syringe showed no significant differences between the control samples and test samples. Provide a safety assessment for the following:
Figure 3 - GC-MS analysis of ABS spike: additional peak at 2.81 minutes
Figure 4 - LC-MS analysis of PC syringe: additional peaks at 7.95, 8.52 larger peak, 9.4, 10.61, 11.69 minutes. We acknowledge that peaks 7.95 and 11.69 appear in the saline control but at a different intensity.
Figure 6 - GC-MS analysis of PC syringe: additional peaks at ~ 1.5 – 2.5 minutes

Submission dated 4/16/2015, eCTD#119/SDN#440 - Response to FDA Information Request – Compatibility of IV Infusion Sets with Treanda liquid – Material of construction other than ABS and PC / PC syringes from various vendors

This submission includes (1) Compatibility data from commonly used IV infusion sets made from materials of construction other than ABS or PC in contact with Treanda liquid in the 0.9% saline infusion solution. (2) Compatibility data from polypropylene syringes supplied various vendors.

A list of IV administration sets and the manufacturers/suppliers includes the following:

B. Braun primary set
B. Braun Secondary set
Baxter Primary set
Baxter primary set with filter
BD Phaseal secondary set
ICU Medical secondary set

Sample Preparation

Saline Control Sample Preparation in IV Bag with Administration Set

1. A 500 mL IV bag of 0.9% sodium chloride was sampled with a syringe and labeled Saline Blank.
2. The IV bag was spiked with the administration set and the tubing was allowed to completely fill with solution and labeled Saline Control (used for appearance only).

Placebo Test Sample Preparation in IV Bag with Administration Set

1. A 3 mL syringe fitted with an 18 gauge needle was used to withdraw 2.4 mL placebo and immediately injected into a 500 mL IV bag of 0.9% sodium chloride. The bag was inverted ten times to mix well.
2. The bag was spiked with an administration set and the tubing was allowed to fill completely. The flow was halted with the wheel clamp that is an integrated component of the administration set. The solution was held in the administration set for 180 minutes on a lab bench at ambient temperature. After 180 minutes, the IV bag was sampled directly using a syringe and labeled Placebo Control Sample.
3. The administration set was then drained from the spike to the end of the tubing and collected in a clean glass container and labeled Placebo Test Sample.

RESULTS

1. Appearance - All appearance results for Treanda placebo stored in the administration sets for up to 180 minutes demonstrated no cloudiness or visible particles.

2. Organic Impurities by Liquid Chromatography-Mass Spectrometry (LC-MS) - A comparison of the total ion chromatograms (TIC) of the placebo control versus the placebo test samples that were stored for 180 minutes showed no new peaks.

3. Organic Impurities by Gas Chromatography-Mass Spectrometry GC-MS - GC-MS analysis of volatile and semi-volatile analytes in the placebo control versus the placebo test samples that were stored for 180 minutes showed no new peaks. One additional peak at 10.35

minutes was noted in both the placebo test and placebo control samples for the B. Braun primary and secondary administration sets. This peak at 10.35 minutes corresponds to diethyl phthalate (DEP) which is a common component of PVC.

Teva's Conclusion

Based on the results generated by visual examination, organic impurities by LC-MS and GC-MS testing, the compatibility of Treanda liquid with IV administration sets has been demonstrated for all manufacturers studied. No differences were noted between the control samples and test samples after exposure for 180 minutes. Based on these studies, it is recommended that the IV administration sets listed in Table 7 may be used with diluted Treanda liquid.

Table 7: IV Administration Sets Recommended for Use with Treanda liquid

Manufacturer/ supplier	Device	Reference number
B. Braun	Primary administration set	NF3482
B. Braun	Secondary administration set	V1921
Baxter	Primary administration set	2C7575
Baxter	Primary administration set with filter	2H8480
BD Phaseal	Secondary administration set	515301
ICU Medical	Secondary administration set	CH3011

Evaluation: Not satisfactory. Results of organic impurities detected by LC-MS and GC-MS testing of the placebo (containing excipients N,N-dimethylacetamide (DMA) 66% vol/vol and propylene glycol, 34% vol/vol.) diluted in 500 mL 0.9% saline and exposed to IV infusion sets shows multiple unidentified peaks. No peak integration was performed so no quantitative estimate of individual and total amount of leachables was included in the submission. Results of visual examination were acceptable and did not exhibit any cloudiness or visible particulates.

IR to the applicant:

Table 6 includes a summary of the organic impurities by GC-MS of the placebo test sample (placebo diluted in 0.9% sodium chloride) and placebo control sample after being held in the IV administration set for 180 minutes. We do not agree with your conclusion that the GC-MS chromatograms placebo test samples are comparable to the placebo control samples. Provide a safety assessment for the following additional peaks identified in the figures below.

Figure 8 - B. Braun Primary Set: Peaks at 1 - ~2 minutes
Figure 11 – B. Braun Secondary Set: Peaks at 0 - ~2.5 minutes
Figure 12 – Baxter Primary Set: Peaks at 0 - ~3 minutes
Figure 13 – Baxter Primary Set with Filter: Peaks at 1 – ~2.5 minutes

Figure 14 – BD Phaseal Secondary Set: Peaks at 1 – ~2.5 minutes
Figure 15 – ICU Medical Secondary Set: Peaks at 1 – ~2.5 minutes

1. Determine compatibility of polypropylene syringes from various vendors with Treanda liquid.

Teva's Response: Initial determination of suitability of BD polypropylene (PP) syringes (Becton Dickinson, Franklin Lakes, NJ, USA) was demonstrated during in-use studies performed for Treanda liquid product during development. Additional studies were performed to determine the compatibility of BD polypropylene 5 mL syringes with metal needles with Treanda liquid product which contains N,N-Dimethylacetamide (DMA).

Additional testing of disposable polypropylene (PP) syringes was conducted using two lots of syringes from each of six different manufacturers to demonstrate compatibility with Treanda liquid. Compatibility was determined via the following testing: appearance, organic impurities, and particulate matter.

The syringes with corresponding needles examined in this study are presented in Table 1.

Table 1: Syringes and Corresponding Needles from Six Manufacturers

Manufacturer	Devic	Ref #	Material of Construction
Becton Dickinson (BD)	5 mL syringe 18 G 1" needle	309646 305195	Polypropylene, thermoelastomer plunger,
Covidien Monoject	5 mL syringe 18 G 1" needle	1180600777 1188818100	Polypropylene, thermoelastomer plunger
B. Braun	5 mL syringe 18 G 1" needle	4617053V-02 4650018-02	Polypropylene, thermoelastomer plunger
Air-Tite Norm Ject	5 mL syringe 18 G 1" needle	4K06048 8300012773	Polypropylene, thermoelastomer plunger
Medline	5 mL syringe 18 G 1" needle	SYR105010 SYRS100185	Polypropylene, thermoelastomer plunger
Terumo	5 mL syringe 18 G 1" needle	SS-05L SG3-1825	Polypropylene, thermoelastomer plunger

2. Study Design

2.1. Study 1 (first lot of syringes and needles)

2.1.1. Determination of Appearance and Organic Impurities

A 5 mL sample of Treanda placebo was filled into each 5 mL polypropylene syringe. The syringes were labeled with appropriate identification, stored on a lab bench at ambient room temperature, for 120 minutes.

2.1.2. Particulate Matter Testing

Particulate matter, USP<788> testing was also performed by transferring Treanda liquid by polypropylene syringe to IV bags containing 0.9% sodium chloride solution (500 mL bag) at the high dose (0.7 mg/mL). Samples were tested after being held for 120 minutes.

2.2. Study 2 (2nd Lot of Syringes & Needles)

2.2.1. Determination of Appearance and Organic Impurities

A second lot of needles and syringes were used to investigate the variability between lots of polypropylene syringes by manufacturer. In addition, a saline control was exposed to the syringes for comparison purposes with regards to potential leachables from the syringe and needle combination. Samples of the bulk saline and bulk placebo were analyzed as control samples.

A 5 mL sample of Treanda drug product placebo or saline was filled into 5 mL disposable polypropylene syringes fitted with a stainless steel needle. The syringes were labeled with appropriate identification, stored on a lab bench at ambient room temperature, and tested after being held for 120 minutes.

2.2.2. Particulate Matter Testing

Particulate matter, USP<788> testing was performed by filling Treanda drug product into 5 mL polypropylene syringes which were stored on a lab bench at ambient room temperature, then diluted into the 0.9% saline 500 mL IV bag. Samples were tested after being held for 120 minutes.

RESULTS

1. **Appearance**

Study 1 (first lot of syringes and needles) - All appearance results for Treanda placebo stored in the polypropylene syringes for up to 120 minutes demonstrated no cloudiness or visible particles.

Study 2 (second lot of syringes and needles) - All appearance results for Treanda placebo stored in the polypropylene syringes for up to 120 minutes demonstrated no cloudiness or visible particles.

2. Organic Impurities by Liquid Chromatography-Mass Spectrometry LC-MS

Study 1 (first lot of syringes and needles) - A comparison of the total ion chromatograms (TIC) of the placebo control sample versus the placebo test samples that were stored in polypropylene syringes for 120 minutes showed only one significant peak at retention time 16.42 minutes in one of the syringes studied (B. Braun). This peak was identified as oleamide is sometimes used in the syringe barrel as a lubricant, and was estimated to be present at > 0.6 ppm based on a 0.6 ppm reserpine external standard. Minor unknown compounds were detected in the 120 minute placebo samples that were absent in the placebo control. However, the signals for these unknowns were less than that which was observed for a 0.6 ppm reserpine external standard. At < 0.6 ppm, these unknown compounds do not represent a safety concern. A representative chromatogram of the control and 120 minute samples for placebo sample, placebo control and the external reference standard illustrates that no additional significant peaks were observed.

Table 9: Organic Impurities by LC-MS Results – Study 1

Sample	Placebo	Placebo test 120
BD	Figure 1	Comparable to control (see Figure 1); minor additional peaks at 4.14, 11.81, 14.36, and 16.93 minutes estimated to be present at < 0.6 ppm based on an external standard
Covidien	Figure 2	Comparable to control (see Figure 2); minor additional peaks at 10.91, 12.45, 15.99 and 16.54 minutes estimated to be present at < 0.6 ppm based on an external standard
B. Braun	Figure 3	Comparable to control (see Figure 3); one significant peak at retention time 16.42 minutes estimated to be present at > 0.6 ppm based on an external standard; minor additional peaks at 10.90, 12.89, 14.75, 16.05, and 17.81 minutes estimated to be present at < 0.6 ppm based on an external standard
Air-Tite	Figure 4	Comparable to control (see Figure 4); minor additional peaks at 10.90 and 16.42 minutes estimated to be present in < 0.6 ppm based on an external standard
Medline	Figure 5	Comparable to control (see Figure 5); minor additional peaks at 7.24, 8.76, 10.90, 14.69, 16.42, and 17.89 minutes estimated to be present in < 0.6 ppm based on an external standard
Terumo	Figure 6	Comparable to control (see Figure 6)

1 Sample not exposed to syringe (bulk solution)

Study 2 (second lot of syringes and needles)

A comparison of the total ion chromatograms (TIC) of the placebo control sample versus the placebo test samples that were stored in polypropylene syringes for 120 minutes showed only one significant peak at retention time 16.42 minutes in two of the syringes studied (B.Braun, and Air-Tite). In study 1, this peak was identified as oleamide which is sometimes used in the syringe barrel as a lubricant, and was estimated to be present at > 0.6 ppm in the B. Braun syringe. In this study, an oleamide external reference standard at 10 ppm was used to

quantify the level of oleamide as approximately 20 ppm in the B. Braun syringe. One additional unknown peak at 16.09 was noted in the B. Braun syringe at < 1 ppm.

The results for all syringes appear in Table 10 of the submission. Minor unknown compounds were detected in the 120 minute placebo samples that were absent in the placebo control. However, the signals for these unknowns were less than that which was observed for a 0.5 ppm reserpine external standard. According to the applicant, at < 0.5 ppm, these unknown compounds do not represent a safety concern, and these polypropylene syringes are acceptable for use with Treanda liquid.

Organic Impurities by Gas Chromatography-Mass Spectrometry (GC-MS)

Study 1 (first lot of syringes and needles)

GC- MS analysis of volatile and semi-volatile analytes in the placebo control sample versus the placebo test samples that were stored in polypropylene syringes for 120 minutes showed only one significant peak at retention time 14.37 in two of the syringes studied (B. Braun and Air- Tite). This peak was identified as oleamide which is sometimes used in the syringe barrel as a lubricant, and was estimated to be present at approximately 12 ppm (B.Braun) and approximately 7 ppm (Air-Tite) based on a BHT external standard of 4 ppm. The results appear in Table 11 of the submission.

Study 2 (second lot of syringes and needles)

GC- MS analysis of volatile and semi-volatile analytes in the placebo control sample versus the placebo test samples that were stored in polypropylene syringes for 120 minutes showed only one peak at retention time 14.24 minutes in two of the syringes studied (B.Braun and Air-Tite). This peak was identified as oleamide which is sometimes used in the syringe barrel as a lubricant, and was estimated to be present at approximately 15 ppm (B.Braun) and approximately 2 ppm (Air-Tite) based on a BHT external standard of 4 ppm. The results appear in Table 12 of the submission.

Particulate Matter, USP <788>

Study 1 (first lot of syringes and needles)

Particulate matter, USP<788> testing was also performed by transferring Treanda liquid by polypropylene syringe to IV bags containing 0.9% sodium chloride solution (500 mL bag) at the high dose (0.7 mg/mL). Samples were tested according to the protocol presented in Table 4. The results presented in Table 13 are all acceptable and demonstrate that no solublized extracts from the polypropylene syringes have precipitated in the infusion bags.

Study 2 (first lot of syringes and needles)

Particulate matter, USP<788> testing was also performed by transferring Treanda liquid by polypropylene syringe to IV bags containing 0.9% sodium chloride solution (500 mL bag) at the high dose (0.7 mg/mL). Samples were tested according to the protocol presented in Table 6 . The results presented in Table 14 are all acceptable and demonstrate that no solublized extracts from the polypropylene syringes have precipitated in the infusion bags.

4. CONCLUSION

Based on the results generated by visual examination, organic impurities by LC-MS and GC-MS testing, and particulate matter testing, the compatibility of Treanda liquid with polypropylene syringes with metal needles has been demonstrated for all manufacturers studied. No significant differences were noted between the control samples and placebo samples stored in the polypropylene syringes from BD, Covidien, Medline, and Terumo for 120 minutes. Oleamide which is sometimes used in the syringe barrel as a lubricant, was detected at up to 7 ppm in the Air-Tite syringes and up to 20 ppm in the B. Braun syringes.

Samples of Treanda liquid stored in the polypropylene syringes for 120 minutes and then transferred to IV bags produced acceptable results when tested for particulate matter, USP <788>. Based on these studies, it is recommended that the polypropylene syringes listed in Table 15 with metal needles be used to transfer Treanda liquid from the vial to the IV bags.

Table 15: Syringes and Corresponding Needles from Six Manufacturers

Manufacturer	Device	Ref #	Material of Construction
Becton Dickenson (BD)	5 mL syringe 18 G 1" needle	309646 305195	Polypropylene, thermoelastomer plunger, Stainless steel, polypropylene hub
Covidien Monoject	5 mL syringe 18 G 1" needle	1180600777 1188818100	Polypropylene, thermoelastomer plunger Stainless steel, polypropylene hub
B. Braun	5 mL syringe 18 G 1" needle	4617053V-02 4650018-02	Polypropylene, thermoelastomer plunger Stainless steel, polypropylene hub
Air-Tite Norm Ject	5 mL syringe 18 G 1" needle	4K06048 8300012773	Polypropylene, thermoelastomer plunger Stainless steel, polypropylene hub
Medline	5 mL syringe 18 G 1" needle	SYR105010 SYRS100185	Polypropylene, thermoelastomer plunger Stainless steel, polypropylene hub
Terumo	5 mL syringe 18 G 1" needle	SS-05L SG3-1825	Polypropylene, thermoelastomer plunger Stainless steel, polypropylene hub

Evaluation: Not satisfactory. Results of organic impurities by LC-MS and GC-MS testing, showed multiple unidentified peaks in the undiluted placebo stored in polypropylene syringes for 120 minutes. Samples of undiluted placebo stored in the polypropylene syringes for 120 minutes and then transferred to IV bags produced acceptable results when tested for particulate matter, USP <788>.

IR to the applicant:

Tables 9 (study 1) and 10 (study 2) include a summary of the organic impurities detected by LC-MS after exposure to the undiluted placebo and saline control in the syringe. Provide a safety assessment for the additional peaks observed in the placebo test samples listed in tables 9 and 10.

Submission dated 6/01/2015, eCTD#126/SDN#457 - Response to FDA Information Request – Compatibility of commonly used gloves with Treanda liquid

The purpose of this response is to provide the compatibility data from commonly used gloves with Treanda liquid.

TEVA RESPONSE:

1. INTRODUCTION

The compatibility of disposable gloves with Treanda liquid was investigated. The qualitative compatibility was determined by application of placebo solution (66% DMA/34% PG) to the glove surface for 10 minutes followed by a visual evaluation of any solution breakthrough or evidence of deformation. All gloves that passed the initial qualitative screening were evaluated for permeability. The permeability evaluation consisted of measuring the presence or absence of bendamustine by HPLC after exposure of each glove material to Treanda liquid for 10 minutes.

2.2. Methods

2.2.1. Appearance (visual inspection)

Gloves are inspected visually for any deformation and/or evidence of solution breakthrough after 10 min of exposure to the placebo solution.

2.3. Glove Evaluation

2.3.1. Procedure for Qualitative Screening of Gloves

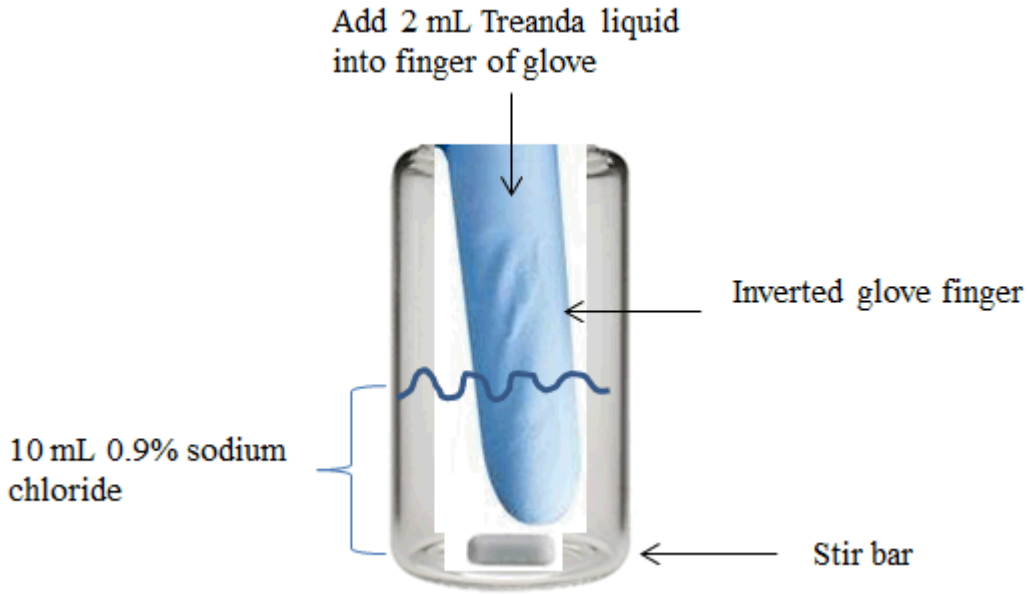
Each glove was screened using the following procedure:

1. A 10 cm x10 cm stainless steel plate and a 9 cm x 9 cm filter paper were inserted inside the glove (palm area).
2. Two mL of placebo solution was spread drop wise on to the glove above the 9 cm x9 cm area.
3. After 10 minutes, the placebo solution was removed with a paper towel and the surface of the glove was wiped dry.
4. The filter paper was removed and inspected for wetness as evidence of product breakthrough.
5. Any change in glove appearance (swelling, wrinkling, or hardening) was noted.

2.3.2. Procedure for Permeability Evaluation of Gloves: Presence or Absence of Bendamustine

Gloves which did not show any evidence of breakthrough from the qualitative screening were evaluated for permeability. All samples were tested for the presence or absence of bendamustine by HPLC. The experimental design for this evaluation is presented in Figure 1. Each glove was evaluated in triplicate. Any glove with a result above the limit of detection (LOD, 14 ng/mL) for bendamustine was considered incompatible.

Figure 1: Permeability Evaluation Method in Scintillation Vial



1. A stir bar and 10 mL of 0.9% sodium chloride are added to the 20 mL vial.
2. A finger of glove material is cut off each glove, inverted, and suspended into a scintillation vial by stretching the end over the rim of the vial.
3. A sample of the 0.9% sodium chloride is analyzed as a blank for the absence of bendamustine.
4. The inverted finger is filled with 2 mL of Treanda liquid.
5. The sodium chloride is stirred using a magnetic stir plate. After 10 minutes of exposure, the glove finger is removed and a sample of the sodium chloride is filled into an HPLC vial. These samples are analyzed for the presence or absence of bendamustine by HPLC.

3. RESULTS

3.1. Qualitative Screening

The results of the qualitative screening of gloves appear in Table 3. The gloves that were negative for the qualitative screening were then evaluated for permeability.

Table 3: Results of Qualitative Screening of Various Glove Brands

Trademark name	Manufacturer	Material	Qualitative screen results for filter wetness	Permeability
CareMate	Shepard Medical	Nitrile	Positive	NT
ChemoPlus	Covidien	Latex	Negative	Compatible
ChemoPlus	Covidien	Nitrile	Negative	Not compatible
DermaFree	Microflex	Vinyl	Positive	NT
EP-Blue	Innovative Healthcare Corporation	Latex	Negative	Compatible
Jackson Safety G29	Kimberly Clarke	Neoprene	Negative	Compatible
NeoGuard	Microflex	Chloroprene	Negative	Not compatible
NeoPro	Microflex	Chloroprene	Negative	Compatible
NitriDerm	Innovative Healthcare Corporation	Nitrile	Negative	Compatible
Purple	Halyard	Nitrile	Negative	Compatible
Purple KC 500	Kimberly Clarke	Nitrile	Negative	Compatible
SafeGrip	Microflex	Latex	Negative	Not compatible
Supreno EC	Microflex	Nitrile	Negative	Not compatible
Ultra One	Microflex	Latex	Negative	Not compatible
UltraSense EC	Microflex	Nitrile	Negative	Compatible
VersaPRO	Medical Specialties Distributors	Vinyl	Positive	NT
Xceed	Microflex	Nitrile	Positive	NT

NT: Not tested since the glove failed the qualitative screen for filter wetness

3.2. Permeability Evaluation

Based on the results of the qualitative screening, permeability evaluation of gloves was performed. The results appear in Table 4. The results indicate that several brands of gloves are compatible, and are acceptable for use with Treanda liquid.

Table 4: Results of the Permeability Evaluation of Various Glove Brands

Trademark name	**Manufacturer**	**Materials**	**Permeability Results (LOD = 14 ng/mL)**	**Comments**
ChemoPlus	Covidien	Latex	< LOD	Compatible
ChemoPlus	Covidien	Nitrile	> LOD	Not compatible
EP-Blue	Innovative Healthcare Corporatio	Latex	< LOD	Compatible
Jackson Safety G29	Kimberly Clarke	Neoprene	< LOD	Compatible
NeoGuard	Microflex	Chloroprene	> LOD	Not compatible
NeoPro	Microflex	Chloroprene	< LOD	Compatible
NitriDerm	Innovative Healthcare Corporatio	Nitrile	< LOD	Compatible
Purple	Halyard	Nitrile	< LOD	Compatible
Purple KC 500	Kimberly Clarke	Nitrile	< LOD	Compatible
SafeGrip	Microflex	Latex	> LOD	Not compatible
Supreno EC	Microflex	Nitrile	> LOD	Not compatible
Ultra One	Microflex	Latex	> LOD	Not compatible
UltraSense EC	Microflex	Nitrile	< LOD	Compatible

4. CONCLUSION

Based on the results of the qualitative screening and the permeability evaluation, it was found that several brands of gloves are acceptable for use with Treanda liquid. The brands that were found to be acceptable are presented in Table 5.

Table 5: Glove Brands found to be Acceptable for Use with Treanda liquid

Trademark name	Manufacturer	Material	Thickness (mil)	Reference number
ChemoPlus	Covidien	Latex	18	CT0194-1
EP-Blue	Innovative Healthcare Corporatio	Latex	13	181350
Jackson Safety G29	Kimberly Clarke	Neoprene	12	49824
NeoPro	Microflex	Chloroprene	6.7	NPG-888
NitriDerm	Innovative Healthcare Corporatio	Nitrile	5	182350
Purple	Halyard	Nitrile	5.9	50604
Purple KC 500	Kimberly Clarke	Nitrile	5.9	55084
UltraSense EC	Microflex	Nitrile	4.7	USE-880

Evaluation: Satisfactory. Agree with Teva's conclusion that the gloves listed in Table 5 are compatible with Treanda injection. Table 6 includes a resorting the information based on the glove thickness. With the exception of vinyl gloves, the compatibility of the glove with Treanda is based on the glove manufacturer and not the composition (nitrile, latex, or chloroprene) of the glove. Vinyl gloves are not compatible with Treanda liquid. For example, results show some nitrile gloves can be used while others cannot depending on the glove manufacturer. Included below is a table of acceptable gloves for use with Treanda based on actual testing of the glove. I will forward you the review once completed.

Glove material	Breakthough Results		Permeability Results	
	Yes (placebo breakthough)	No (no breakthrough)	Compatible	Not compatible
Chloroprene	**0**	**2**	**1**	**1**
Latex	**0**	**4**	**2**	**2**
Neoprene	**0**	**1**	**1**	**0**
Nitrile	**2**	**6**	**2**	**4**
Vinyl	**2**	**0**	**NT**	**NT**

NT: not tested

Submission dated 6/04/2015, eCTD#127/SDN#459 - Determine compatibility of Closed System Transfer Device (CSTD) from various vendors with Treanda liquid

TEVA'S RESPONSE:

1. INTRODUCTION

This evaluation was performed using placebo filled into clear vials. Each manufacturer's CSTD system consists of multiple components which were evaluated stepwise. At each step, if physical compatibility was confirmed visually, then the next step was performed. If an entire CSTD system was physically compatible by visual evaluation, and passed particulate matter, USP<788>, leachables testing was performed on the diluted placebo dispensed from the administration set. Compatibility was determined by appearance, particulate matter, and organic impurities as measured by LC/MS and GC/MS. After the evaluation with placebo was completed, the compatible CTSDs were evaluated with Treanda liquid for visual appearance and particulate matter, USP<788>.

The following CSTD were used in the study:

Becton Dickenson (BD) Phaseal
Teva Tevadaptor
ICU Medical
Carefusion
Equashield

2. STUDY DESIGN USING TREANDA DRUG PRODUCT

Any CTSD complete system that was found to be compatible with placebo was evaluated using Treanda liquid. At each step, all samples were inspected for visual clarity and the final solution from the IV bag was analyzed for particulate matter by USP <788>. Each system was prepared and evaluated in triplicate.

3. RESULTS

3.1. Appearance

The CSTD system components were inspected visually for any deformities/abnormalities and samples were inspected for cloudiness or visible particles in the solution. A visual inspection was performed at each step as described in the procedures for each CSTD studied. Only the BD Phaseal passed the appearance tests.

Table 2: Appearance Results for CSTDs Studied

CSTD	Control description	Sample description (step)
Becton Dickenson (BD) Phaseal		
Device	No abnormalities or visible defects	No change
Sample solution	Clear, colorless liquid, no visible	No change
Teva Tevadaptor		
Device	No abnormalities or visible defects	No change
Sample solution	Clear, colorless liquid, no visible particles	Cloudy with visible particles
ICU Medical		
Device	No abnormalities or visible defects	No change
Sample solution	Clear, colorless liquid, no visible	Translucent, hazy (step 4)
Carefusion		
Device	No abnormalities or visible defects	No change
Sample solution	Clear, colorless liquid, no visible particles	1of 6 device failure (step 3)
Equashield		
Device	No abnormalities or visible defects	No change
Sample solution	Clear, colorless liquid, no visible particles	No change, failed particulate matter

3.2. Organic impurities by LC-MS

Based on the results of the appearance testing (see Table 2), testing by LC-MS was performed on only the BD Phaseal CSTD. A comparison of the total ion chromatograms (TIC) of the CSTD placebo test sample, the CSTD saline control sample, and placebo control showed no new significant peaks.

3.3. Organic impurities by GC-MS

Based on the results of the appearance testing (see Table 2), organic impurity testing by LC-MS was performed on only the BD Phaseal CSTD. GC-MS analysis of volatile and semi-volatile analytes in the CSTD placebo test sample solutions yielded no peaks observed that were not in the placebo control or the CSTD saline control sample. The results appear in Table 4. Representative chromatograms which illustrates that no additional peaks were observed are presented in Figure 12.

Table 4: Organic Impurities by GC-MS Results for BD Phaseal CSTD

	BD Phaseal

	Initial	3 Hours
Saline control	See Figure 12	NT
Placebo control	See Figure 12	NT
Placebo test sample	NT	Comparable to control, see Figure

NT = Not Tested, as per the study design

3.4. Particulate Matter

Based on the results of the appearance testing, particulate matter, USP<788> testing was also performed by transferring Treanda liquid utilizing the BD Phaseal CSTD to IV bags containing 0.9% sodium chloride solution (500 mL bag) at the high dose (0.7 mg/mL). The results presented in are acceptable and demonstrate that no solublized extracts from the BD Phaseal CSTD have precipitated in the infusion bags.

4. CONCLUSION

Based on the results generated by visual examination, organic impurities by LC-MS, GC-MS, and particulate matter testing the compatibility of Treanda liquid was demonstrated for only one of the five CSTDs studied. Only the BD Phaseal CSTD was found to be compatible with Treanda liquid (see Table 6).

Table 6: Compatibility of CSTDs for Use with Treanda liquid

CSTD	Use with Treanda liquid
Becton Dickenson (BD) Phaseal	Compatible
Teva Tevadaptor	Not
ICU Medical	Not
Carefusion	Not
Equashield	Not

Evaluation: Not satisfactory. Agree with the applicant that the Teva Tevadaptor, ICU Medical, Carefusion, and Equashield are not compatible with Treanda injection. There are multiple unidentified peaks at unknown levels in the chromatograms for Becton Dickenson (BD) Phaseal.

IR to the applicant:

We do not agree with your conclusion that the GC-MS analysis of volatile and semi-volatile analyses in the CSTD placebo test sample solutions yielded no peaks observed that were not in the placebo control or the CSTD saline control sample. Provide a safety assessment for the additional peaks observed in figure 12 at ~ 1-2 minutes.

Submission dated 7/9/2015, eCTD#132/SDN#471 - Response to FDA Information Request Compatibility Study – Polypropylene syringes from various vendors

FDA'S QUESTION 1 :

Regarding the April 16, 2015 submission – Compatibility of IV Infusion Sets with Treanda liquid – Material of construction other than ABS and PC syringes from various vendors. Determine the compatibility of polypropylene syringes from various vendors with Treanda liquid.

a. Provide a tabular listing of individual and total levels of the peaks listed in tables 9 and 10, along with the identity of each leachable (if possible).

Teva's Response:

A tabular listing of individual levels of the peaks listed in Tables 9 (study 1) and Table 10 (study 2), in the determination of compatibility of polypropylene syringes from various vendors with Treanda liquid is provided in Table 1. In study 1, a comparison of the total ion chromatograms (TIC) of the placebo control sample versus the placebo test samples that were stored in polypropylene syringes for 120 minutes showed only one significant peak at retention time 16.42 minutes in one of the syringes studied (B. Braun). This peak was identified as oleamide which is sometimes used in the syringe barrel as a lubricant, and was estimated to be present at > 0.6 ppm based on a 0.6 ppm reserpine external standard. For all syringes evaluated, minor unknown compounds were detected in the 120 minute placebo test samples that were absent in the placebo control. However, the signals for these unknowns were less than that which was observed for a 0.6 ppm reserpine external standard.

In study 2, a comparison of the total ion chromatograms (TIC) of the placebo control sample versus the placebo test samples that were stored in polypropylene syringes for 120 minutes showed only one significant peak at retention time 16.44 minutes in two of the syringes studied (B.Braun, and Air-Tite). In study 1, this peak was identified as oleamide and was estimated to be present at > 0.6 ppm in the B. Braun syringe. In this study, an oleamide external reference standard at 10 ppm was used to quantify the level of oleamide as approximately 20 ppm in the B. Braun syringe and approximately 4 ppm in the Air-Tite syringe. A 0.5 ppm and 1.0 ppm reserpine external standard was used to approximate the level of all other unknowns.

Evaluation: Acceptable.

b. The results presented in tables 9 and 10 show more leachables in table 9. Confirm that the same methodology was used in your analysis and explain the difference between the two data sets.

Teva's response: The same methodology was used for the analysis in study 1 (Table 9) and study 2 (Table 10). The only differentiation being that different lots of syringes were used from each manufacturer. Approximately the same number of unknowns has been noted for each manufacturer in study 1 and 2, (see Table 1) with the exception of Covidien, which had no unknowns in study 2 that did not appear in the control samples. Differences in unknown peaks seen can be attributed to the very low levels present (< 1 ppm) and the lot to lot variability of the manufacturers' syringes.

Evaluation: Acceptable.

Submission dated 7/10/2015, eCTD#133/SDN#472 – Compatibility of commonly available vial adaptors with Treanda liquid.

NDA 22249/S-021, TREANDA (bendamustine hydrochloride) Injection

This submission provides compatibility data from commonly available vial adaptors that are not made of ABS or PC when used with Treanda liquid. The data provided in this submission is from the final study as outlined in the March 18th proposed compatibility study plan.

Method: Samples were prepared using Treanda placebo and each vial adapter. For each vial adapter, compatibility at each step was assessed visually before proceeding to the next step. If visual compatibility was confirmed for all steps, a sample was prepared using Treanda liquid and collected from the end of the administration set and analyzed for particulate matter via USP<788>. If the solution from the IV bag conformed to USP<788>, then a sample from a bag prepared with placebo was analyzed for organic impurities by LC/MS and GC/MS. All samples were prepared in triplicate.

Results demonstrate that the vial adapters listed as compatible in table 1 can be used with Treanda injection.

Table 1: Vial Adapter Compatibility with Treanda injection

Vial adapter	**Use with Treanda injection**
Baxter CHEMO- AIDE	Compatible
Medimop	Compatible
Alaris Products 2202E	Compatible
Alaris Products 2203E	Compatible
Baxter Interlink	Incompatible
B Braun	Incompatible
CareFusion	Incompatible
MedStream	Incompatible

Evaluation: Satisfactory. Agree with Teva's assessment of the acceptability of the Baxter CHEMO- AID, Medimop, Alaris Products 2202E, and Alaris Products 2203E for use with Treanda injection.

Submission dated 8/20/2015, eCTD#136/SDN#477: New Labeling Supplement

Evaluation: Teva agreed to all of the Agency's proposed revisions and submitted the revised USPI and DHCP letter officially to the pending Supplement S-021. CMC has no further revisions to the labeling.

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/s/

JANICE T BROWN
08/27/2015

ILAN GEERLOF-VIDAVSKY
08/27/2015

HASMUKH B PATEL
08/27/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022249/S-21

OTHER REVIEW(S)

Safety Team Memo - TSI Review

Re:	TSI 1368
NDA#	22249
Product Name	Treanda
Sponsor	Teva
Office/Division	OND/OHOP/DHP
Safety RPM	Diane Leaman
Medical Officer for Safety	Qin Ryan, MD, PhD
Date Review Completed	August 28, 2015

1. Issue

To assess the compatibility of Treanda Injection with various devices, to revise the labeling for the communication of device compatibility, and to generate Dear Healthcare Provider Letter, and a Proposal for Maintaining the List of Compatible Devices

2. Summary and Recommendations:

After reviewing the following NDA supplements (see Dr. Brown's CMC review dated August 26, 2015 for details):

1. NDA 22249/S-015 - New liquid formulation of Treanda, Treanda injection
2. NDA 22249/S-019 (Labeling Supplement – Data supporting the use of closed system transfer devices, vial adapters, polypropylene syringes, disposable gloves and IV administration sets) .
3. NDA 22249/S-021 – Labeling supplement. Communication of device compatibility, Dear Healthcare Provider Letter, and Proposal for Maintaining the List of Compatible Devices

The Agency OPQ review team, working closely with the DHP clinical and safety teams, analyzed the data regarding the compatibility of Treanda Injection with various devices, revised and negotiated revisions to the product labeling to inform the healthcare community about the safety issue when using Treanda with devices containing ABS, including a listing of certain devices that could be used safely with Treanda. The Agency also reviewed and revised the Applicant's generate Dear Healthcare Provider Letter, and finalized a Proposal for Maintaining the List of Compatible Devices. The DMEPA team reviewed and agreed with the finalized labeling, detailed in Dr. Malsov's review memo dated August 25, 2015.

Therefore, the DHP safety team believes the TSI 1368 can be closed because the safety issue under this TSI has been adequately addressed.

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/s/

QIN C RYAN
09/01/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 25, 2015
Requesting Office or Division:	Division of Hematology Products
Application Type and Number:	NDA 22249/S-21; TSI #1368
Product Name and Strength:	Treanda (Bendamustine Hydrochloride) Injection, 45 mg /0.5 mL and 180 mg/2 mL (90 mg/mL)
Submission Date:	August 20, 2015
Applicant/Sponsor Name:	Teva
OSE RCM #:	2015-355-1
DMEPA's Review Author/Team Leader:	Yelena Maslov, Pharm.D

1 PURPOSE OF MEMO

Division of Hematology Products (DHP) requested that we review prescriber information (PI) labeling and Dear HealthCare Provider Letter to determine if they are acceptable from a medication error perspective. TREANDA Injection is not compatible with CSTDs, adaptors, and syringes containing polycarbonate or ABS. This incompatibility leads to device failure (e.g., leaking, breaking, or operational failure of CSTD components), possible product contamination, and potential serious adverse health consequences to the practitioner, including skin reactions; or to the patient, including but not limited to, the risk of small blood vessel blockage if they receive product contaminated with dissolved ABS or polycarbonate.

2 CONCLUSIONS

We reviewed the proposed PI labeling and Dear HealthCare Provider Letter labeling and conclude that the labels and labeling are acceptable to DMEPA from the medication errors standpoint. Thus, we have no additional recommendations at this time.

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/s/

YELENA L MASLOV
08/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022249/S-21

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, August 25, 2015 10:04 AM
To: Mike McGraw (Mike.McGraw@tevapharm.com)
Cc: Carioti, Theresa; Scott, Kimberly
Subject: NDA 22249 S 021 Treanda: FDA Edits DHCP letter: DUE today
Attachments: NDA 22249 FDA edits DHCP letter.docx; NDA 22249 FDA agreed USPI.doc

Importance: High

Tracking:

Recipient	Read
Mike McGraw (Mike.McGraw@tevapharm.com)	
Carioti, Theresa	
Scott, Kimberly	Read: 8/25/2015 10:07 AM

Hi Mike,

Please refer to your supplement NDA 22249, S-021 submitted August 20, 2015, and received on August 20, 2015. The FDA team has reviewed the proposed USPI and DHCP letter, and we have accepted all changes in the Treanda PI, and have attached a clean version. This represents the agreed upon labeling. We have also reviewed the DHCP letter and the team has proposed some minor edits.

If Teva agrees to all the Agency's proposed revisions, please submit the USPI and DHCP letter officially to the pending Supplement S-21 (please send me a copy via email). If you propose edits to our changes, please send that response via email by 4:00pm today.

Please confirm receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
09/04/2015
IR to Applicant to revise DHCP letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022249/S-021

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

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:

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:	022249
SUPPLEMENT NUMBER:	0-021
PRODUCT NAME:	TREANDA® (bendamustine hydrochloride) Injection (solution) 45mg/0.5mL or 180mg/2mL TREANDA® (bendamustine hydrochloride) for Injection (lyophilized powder), 25 mg/vial or 100mg/vial
DATE OF SUBMISSION:	AUGUST 20, 2015
DATE OF RECEIPT:	AUGUST 20, 2015

This supplemental application proposes the following changes for TREANDA® Injection (solution) :

- Revise the US Prescribing Information for TREANDA in order to communicate new information about the compatibility of TREANDA Injection with devices that is commonly used in the preparation and administration of TREANDA.

- Update the Dear Healthcare Provider letter to communicate compatibility data.

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, please call me at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Kimberly Scott, RN, BSN, OCN®
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KIMBERLY L SCOTT
08/31/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, August 25, 2015 10:04 AM
To: Mike McGraw (Mike.McGraw@tevapharm.com)
Cc: Carioti, Theresa; Scott, Kimberly
Subject: NDA 22249 S 021 Treanda: FDA Edits DHCP letter: DUE today
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Importance: High

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If Teva agrees to all the Agency's proposed revisions, please submit the USPI and DHCP letter officially to the pending Supplement S-21 (please send me a copy via email). If you propose edits to our changes, please send that response via email by 4:00pm today.

Please confirm receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
08/25/2015
USPI agreed changes, edits DHCP letter