

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022249/S-19

Trade Name: **TREANDA**

Generic Name: **Bendamustine Hydrochloride**

Sponsor: **Cephalon, Inc.**

Approval Date: 03/10/2015

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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APPROVAL LETTER



NDA 022249/S-019

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 March 6, 2015, received March 6, 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.

We acknowledge receipt of your submissions related to this NDA dated February 26, March 2, 3, 4, and 6, 2015. We also acknowledge receipt of your amendments to this supplement on March 9 and 10, 2015.

This "Changes Being Effected" supplemental new drug application provides for updates to the United States Prescribing Information (USPI) to include 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-butadiene-styrene (ABS).

We also have the following comments regarding this sNDA approval:

1. Submit quarterly reports until March 2017 of complaints about preparation and use of Treanda injection (solution) and Treanda for injection (lyophilized powder).
2. We remind you of your commitment to continue conducting device compatibility studies with Treanda injection (solution) to ensure safe preparation and use of 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 Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

CARTON AND IMMEDIATE CONTAINER LABELS

Until carton labeling and vial changes are implemented, as an interim measure for the Treanda liquid product that has already been distributed to pharmacies, hospitals, etc., you need to provide stickers/labels that can adhere to the carton labeling with the Treanda liquid product. FDA recommends the following statement on the sticker: “**Not for use with devices that contain polycarbonate or acrylonitrile-butadiene-styrene (ABS)**”. The sticker should be accompanied with the Dear Healthcare Provider (DHCP) letter. Furthermore, the same sticker should be attached to carton and any other appropriate labeling of already existing and ready for shipment product supply at the manufacturers and distributors sites.

Carton Labeling

1. In the proposed statement “Do not use with devices that contain polycarbonate or acrylonitrile butadiene-styrene (ABS)” increase the prominence of negation “NOT,” by using all capital letters or bolding as negative sentences containing NOT can be misinterpreted as the opposite since NOT can be overlooked”.
2. Increase the prominence of the storage information on the side panel by bolding the entire statement “Store refrigerated at....” As storage for Treanda Injection differs from the storage of Treanda for Injection and this information should be easily identified by healthcare providers.

Vial Container

1. We recommend addition of a flag to the actual vial containing a statement “Do not use with devices that contain polycarbonate or acrylonitrile butadiene-styrene (ABS)” on the container. Increase the prominence of negation “NOT,” by using all capital letters or bolding as negative sentences containing NOT can be misinterpreted as the opposite since NOT can be overlooked.

Submit final printed carton and immediate container labels that are identical to the submitted carton and immediate container labels dated March 6, 2015, **except** with the revisions listed above, as soon as they are available, but no more than 7 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022249/S-019.**” Approval of this submission by FDA is not required before the labeling is used.

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

PROPRIETARY NAME

To prevent medication errors related to confusion between the two formulations of bendamustine hydrochloride due to different products’ concentrations, we recommend you consider one of the following options regarding proprietary name:

1. Propose a modifier to be added to the proprietary name Treanda for the injection dosage form to help differentiate the product from the lyophilized powder formulation and submit to the Agency for evaluation. We continue to recommend

against the (b) (4) as stated in proprietary name request unacceptable letter sent to you on June 13, 2013 (see attached).

2. Alternatively, you can propose a dual proprietary name for the injection dosage form. However, if choosing this option, consider retaining a portion of the original Treanda name in the new name (e.g. TreanXXXX) so health care practitioners recognize that this product is associated with, (or an extension of) Treanda.

Please submit a request for review of your proposed proprietary name. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names

[http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

UCM075068.pdf). Further information about how FDA evaluates propriety names for drug products is available in the following guidance, Best Practices in Developing Proprietary Names for Drugs

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>.

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry titled, “Contents of a Complete Submission for the Evaluation of Proprietary Names”, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

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 apply 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, please 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

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

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

/s/

ANN T FARRELL
03/10/2015

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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)	03/2015
Selection of TREANDA Formulation to Administer (2.1)	03/2015
Preparation for Intravenous Administration (2.4)	03/2015
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/m² infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles (2.2)
- Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce dose to 50 mg/m² on Days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m² on Days 1 and 2. (2.2)
- Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m² on Days 1 and 2 of each cycle. (2.2)
- Dose re-escalation may be considered. (2.2)

For NHL:

- 120 mg/m² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles (2.3)
- Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle. (2.3)
- Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle. (2.3)

General Dosing Considerations:

- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥ 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. (6.2)
- Most common hematologic abnormalities for both indications (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. (6.1, 6.2)

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

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

1.2 Non-Hodgkin Lymphoma (NHL)

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

2 DOSAGE AND ADMINISTRATION

2.1 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 with devices containing polycarbonate or acrylonitrile-butadiene-styrene (ABS) including closed system transfer devices (CSTDs), adapters, and syringes.

Only use a polypropylene syringe with a metal needle and polypropylene hub to withdraw and transfer TREANDA Injection. 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 closed system transfer device or adaptor is used as supplemental protection during preparation¹, only use TREANDA for Injection, the lyophilized powder formulation.

2.2 Dosing Instructions for CLL

Recommended Dosage:

The recommended dose is 100 mg/m² administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

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

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

Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m² on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m² on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m² on Days 1 and 2 of each cycle.

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

2.3 Dosing Instructions for NHL

Recommended Dosage:

The recommended dose is 120 mg/m² administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

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

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

Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m² on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m² on Days 1 and 2 of each cycle.

2.4 Preparation for Intravenous Administration

TREANDA 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.

- **Do not use with devices that contain polycarbonate or acrylonitrile-butadiene-styrene (ABS), including most Closed System Transfer Devices (CSTDs).** TREANDA Injection contains N,N-dimethylacetamide (DMA), which is incompatible with devices that contain polycarbonate or ABS. Devices, including CSTDs, adaptors, 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.
- **Only use a polypropylene syringe with a metal needle and a polypropylene hub to withdraw and transfer TREANDA Injection.**
- 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.
- 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 adaptor is to be used as supplemental protection during preparation¹, only use TREANDA for Injection, the lyophilized formulation.

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

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

General Information

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

2.5 Admixture Stability

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

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

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored under refrigerated conditions at 2°-8°C (36°-46°F) or for **2 hours** when stored at room temperature (15°-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/m²) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert). Cases of Stevens-Johnson syndrome (SJS)

and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to TREANDA cannot be determined.

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

5.6 Other Malignancies

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

5.7 Extravasation Injury

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

5.8 Embryo-fetal Toxicity

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

6 ADVERSE REACTIONS

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

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

The data described below reflect exposure to TREANDA in 329 patients who participated in an actively-controlled trial (N=153) for the treatment of CLL and two single-arm trials (N=176) for the treatment of indolent B-cell NHL. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in CLL

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

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

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

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

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

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in $\geq 5\%$ of patients in either treatment group in the randomized CLL clinical study.

Table 1: Non- Hematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

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

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

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

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

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

6.2 Clinical Trials Experience in NHL

The data described below reflect exposure to TREANDA in 176 patients with indolent B-cell NHL treated in two single-arm studies. The population was 31-84 years of age, 60% male, and 40% female. The race distribution was 89% White, 7% Black, 3% Hispanic, 1% other, and <1% Asian. These patients received TREANDA at a dose of 120 mg/m² intravenously on Days 1 and 2 for up to eight 21-day cycles.

The adverse reactions occurring in at least 5% of the NHL patients, regardless of severity, are shown in Table 3. The most common non-hematologic adverse reactions (≥30%) were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%) and pyrexia (34%). The most common non-hematologic Grade 3 or 4 adverse reactions (≥5%) were fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia and dehydration, each reported in 5% of patients.

Table 3: Non-Hematologic Adverse Reactions Occurring in at Least 5% of NHL Patients Treated with TREANDA by System Organ Class and Preferred Term (N=176)

System organ class Preferred term	Number (%) of patients*	
	All Grades	Grade 3/4
Total number of patients with at least 1 adverse reaction	176 (100)	94 (53)
Cardiac disorders		
Tachycardia	13 (7)	0
Gastrointestinal disorders		
Nausea	132 (75)	7 (4)
Vomiting	71 (40)	5 (3)

Diarrhea	65 (37)	6 (3)
Constipation	51 (29)	1 (<1)
Stomatitis	27 (15)	1 (<1)
Abdominal pain	22 (13)	2 (1)
Dyspepsia	20 (11)	0
Gastroesophageal reflux disease	18 (10)	0
Dry mouth	15 (9)	1 (<1)
Abdominal pain upper	8 (5)	0
Abdominal distension	8 (5)	0
General disorders and administration site conditions		
Fatigue	101 (57)	19 (11)
Pyrexia	59 (34)	3 (2)
Chills	24 (14)	0
Edema peripheral	23 (13)	1 (<1)
Asthenia	19 (11)	4 (2)
Chest pain	11 (6)	1 (<1)
Infusion site pain	11 (6)	0
Pain	10 (6)	0
Catheter site pain	8 (5)	0
Infections and infestations		
Herpes zoster	18 (10)	5 (3)
Upper respiratory tract infection	18 (10)	0
Urinary tract infection	17 (10)	4 (2)
Sinusitis	15 (9)	0
Pneumonia	14 (8)	9 (5)
Febrile neutropenia	11 (6)	11 (6)
Oral candidiasis	11 (6)	2 (1)
Nasopharyngitis	11 (6)	0
Investigations		
Weight decreased	31 (18)	3 (2)
Metabolism and nutrition disorders		
Anorexia	40 (23)	3 (2)
Dehydration	24 (14)	8 (5)
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 $\geq 5\%$ of patients were febrile neutropenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or postmarketing experience were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome.

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

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TREANDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: anaphylaxis; and injection or infusion site reactions including phlebitis, pruritus, irritation, pain, and swelling; pneumocystis jiroveci pneumonia and pneumonitis.

Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. [see *Warnings and Precautions (5.5)*]

7 DRUG INTERACTIONS

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.8)]

Risk Summary

TREANDA can cause fetal harm when administered to a pregnant woman. Bendamustine caused malformations in animals, when a single dose was administered to pregnant animals. Advise women to avoid becoming pregnant while receiving TREANDA and for 3 months after therapy has stopped. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to a fetus. Advise men receiving TREANDA to use reliable contraception for the same time period.

Animal data

Single intraperitoneal doses of bendamustine from 210 mg/m² (70 mg/kg) in mice administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (exencephaly, cleft palates, accessory rib, and spinal deformities) and decreased fetal body weights. This dose did not appear to be maternally toxic and lower doses were not evaluated. Repeat intraperitoneal dosing in mice on gestation days 7-11 resulted in an increase in resorptions from 75 mg/m² (25 mg/kg) and an increase in abnormalities from 112.5 mg/m² (37.5 mg/kg) similar to those seen after a single intraperitoneal administration. Single intraperitoneal doses of bendamustine from 120 mg/m² (20 mg/kg) in rats administered on gestation days 4, 7, 9, 11, or 13 caused embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in external [effect on tail, head, and herniation of external organs (exomphalos)] and internal (hydronephrosis and hydrocephalus) malformations were seen in dosed rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The effectiveness of TREANDA in pediatric patients has not been established. TREANDA was evaluated in a single Phase 1/2 trial in pediatric patients with leukemia. The safety profile for TREANDA in pediatric patients was consistent with that seen in adults, and no new safety signals were identified.

The trial included pediatric patients from 1-19 years of age with relapsed or refractory acute leukemia, including 27 patients with acute lymphocytic leukemia (ALL) and 16 patients with acute myeloid leukemia (AML). TREANDA was administered as an intravenous infusion over 60 minutes on Days 1 and 2 of each 21-day cycle. Doses of 90 and 120 mg/m² were evaluated. The Phase 1 portion of the study determined that the recommended Phase 2 dose of TREANDA in pediatric patients was 120 mg/m².

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/m² in the Phase 1 portion of the study.

In the above-mentioned pediatric trial, the pharmacokinetics of TREANDA at 90 and 120 mg/m² 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/m². The exposures (AUC₀₋₂₄ and C_{max}) to bendamustine in pediatric patients following a 120 mg/m² intravenous infusion over 60 minutes were similar to those in adult patients following the same 120 mg/m² 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

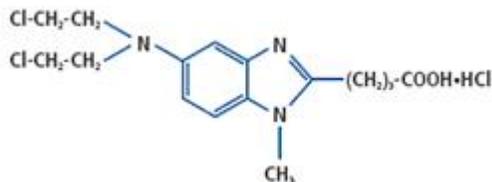
The intravenous LD₅₀ of bendamustine HCl is 240 mg/m² in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

Across all clinical experience, the reported maximum single dose received was 280 mg/m². 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-butyric 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/m² intravenous infusion followed by a 30-minute intravenous infusion of bendamustine at 90 mg/m²/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 dihydroxybendamustine (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 1/10th and 1/100th 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 [¹⁴C] 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/m² bendamustine IV over 1-hour the intermediate $t_{1/2}$ of the parent compound is approximately 40 minutes. The mean apparent terminal elimination $t_{1/2}$ 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/m² 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/m² there was no meaningful effect of mild (total bilirubin \leq ULN, AST \geq ULN to 2.5 x ULN, and/or ALP \geq 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/m²/day (12.5 mg/kg/day, the lowest dose tested) and 75 mg/m²/day (25 mg/kg/day) for four days, peritoneal sarcomas in female AB/jena mice were produced. Oral administration at 187.5 mg/m²/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/m², the lowest dose tested.

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

14 CLINICAL STUDIES

14.1 Chronic Lymphocytic Leukemia (CLL)

The safety and efficacy of TREANDA were evaluated in an open-label, randomized, controlled multicenter trial comparing TREANDA to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

The patient populations in the TREANDA and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean 65.7x10⁹/L vs. 65.1x10⁹/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either TREANDA at 100 mg/m², administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL¹.

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

Table 5: Efficacy Data for CLL

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

CI = confidence interval

* CR was defined as peripheral lymphocyte count $\leq 4.0 \times 10^9/L$, neutrophils $\geq 1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$, 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.

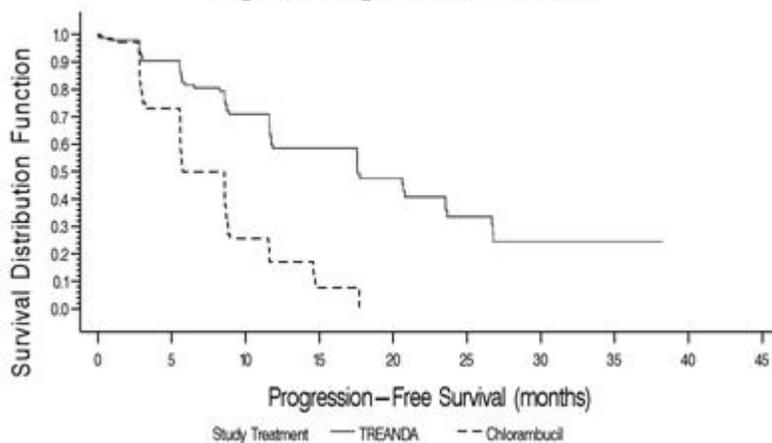
** nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

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

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

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

Figure 1. Progression-Free Survival



14.2 Non-Hodgkin Lymphoma (NHL)

The efficacy of TREANDA was evaluated in a single arm study of 100 patients with indolent B-cell NHL that had progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received TREANDA intravenously at a dose of 120 mg/m^2 , on Days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles.

The median age was 60 years, 65% were male, and 95% had a baseline WHO performance status of 0 or 1. Major tumor subtypes were follicular lymphoma (62%), diffuse small lymphocytic lymphoma (21%), and marginal zone lymphoma (16%). Ninety-nine percent of patients had received previous chemotherapy, 91% of patients had received previous alkylator therapy, and 97% of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab.

Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in Table 6.

Table 6: Efficacy Data for NHL*

	TREANDA (N=100)
Response Rate (%)	
Overall response rate (CR+CRu+PR)	74
(95% CI)	(64.3, 82.3)
Complete response (CR)	13
Complete response unconfirmed (CRu)	4
Partial response (PR)	57
Duration of Response (DR)	
Median, months (95% CI)	9.2 months (7.1, 10.8)

CI = confidence interval

*IRC assessment was based on modified International Working Group response criteria (IWG-RC). Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥ 20 mm.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from TREANDA Injection 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 a solution of TREANDA contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA contacts the mucous membranes, flush thoroughly with water.

TREANDA is a cytotoxic drug. Follow special handling and disposal procedures¹

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-010

Distributed By:

**Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454**

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 022249/S-19

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.

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

/s/

QIN C RYAN
09/01/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 2, 2015
Time: 4:15 PM – 5:00 PM

Application Number: NDA 022249

Product Name: Treanda (Bendamustine HCL)

Applicant Name: TEVA (Cephalon wholly owned subsidiary of TEVA Pharmaceuticals)

Subject: Discuss Teva's edits of USPI label, DHCP letter, and Carton-Container Labels

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Robin Jones, VP, Quality Compliance

1.0 BACKGROUND:

The liquid formulation of Treanda was approved on September 13, 2013. Prior to the marketing of the liquid formulation, there was a lyophilized powder formulation, which was the initial product formulation, approved in 2008.

On February 12, 2015, Division of Drug Information received a complaint from a hospital pharmacist that described a problem with Treanda liquid solution, which included melting of the syringe adaptor hub that caused the Treanda to leak out. A photo of the melted Tevadaptor was provided with the complaint. The pharmacist noted that the new formulation contains the

(b) (4) N, N-dimethylacetamide and that this (b) (4) is not compatible with devices containing polycarbonate.

Teva contacted the Division on February 13, 2015 with a proposed Dear Healthcare Provider letter (DHCP) to describe the risks associated with using close system transfer device with products that contain N, N-Dimethylacetamide.

The Division met internally on February 25, 2015 to discuss the safety issues for Treanda liquid formulation and the next steps for advising the applicant to incorporate necessary labeling changes. The Agency had learned through follow-up information requests to Teva that there have been several reported complaints (at least 45 since December 9, 2014) with the liquid Treanda product and closed system transfer devices; including leaking, melting of the syringe/adaptor hub, cloudy product in bag, etc.

Office of Communications (OCOMM) has been informed of the issues and need for the Agency to issue a safety communication. Center for Devices and Radiologic Health (CDRH), general hospital devices branch, was consulted to discuss the concerns with safety to patients and health care providers and the devices used with Treanda.

The Agency initially requested via email for Teva to submit the current compatibility information for Treanda liquid formulation by Friday, February 27, 2015.

During T-con with Teva on February 27, 2015, Teva agreed to revise DHCP letter, USPI label with both liquid and lyophilized formulations, make revisions to the carton/container labeling. Furthermore, Teva agreed to submit communication plan, compatibility data with Treanda liquid and polypropylene syringes, and a plan for further compatibility studies with proposed timelines. The above was to be submitted to the Agency by Monday, March 2, 2015.

2.0 DISCUSSION:

Based upon discussions with CDER's management; FDA recommends that both forms of Treanda, liquid formulation and lyophilized powder product continue to be marketed to provide access to patients in various health care settings. FDA made specific comments and recommendations for the DHCP letter and labeling.

DHCP letter: FDA advised Teva to add more specific information regarding incompatibility, specifically include details and descriptions of what problems were noted when using CSTD's. Teva should provide direct guidance for HCPs regarding safety, i.e. what to do when a hood is not present, etc. FDA emphasized that the language should be consistent in DHCP and PI Label.

PI Label: Teva provided changes to the label, but FDA reiterated that both the labeling and DHCP letter need to be consistent to decrease confusion for HCPs. The message wasn't consistent with Polycarbonate or Acrylonitrile-butadiene-styrene (ABS) syringes with metal needle. FDA asked Teva what type of needles should be used and further asked do the proposed needles have plastic hubs. FDA stated it's important to provide specific guidance for pharmacists preparing Treanda liquid solution.

FDA discussed data from compatibility Study #1 (Teva provided this data via email to the RPM on the morning of March 2, 2015, see attached), and has required that Teva repeat the study.

Teva proposed a safe alternative to using CSTD would be to use Polypropylene (PP) syringe with metal needle. Teva tells FDA they did compatibility studies with transferring the Treanda solution after 20 minutes without any reactions or problems.

FDA expressed concerns that the PP compatibility study they've provided is not compelling, and that the concern is not all pharmacists are going to immediately withdrawal Treanda liquid product and inject into the bag. FDA tells Teva that the DHCP letter should encompass more of a description of what happens if the wrong type of device is used with Treanda liquid. This suggestion is to better help pharmacists understand the problem with compatibility of certain devices.

FDA inquired about Teva's plans for the lyophilized powder product and liquid formulation. Teva stated they plan is to continue to market the liquid and lyophilized product. (b) (4)



FDA suggested that Teva do US marketing research with the lyophilized powder, and understand the significance of the demand of the Treanda in light of the compatibility problems associated with Treanda liquid. FDA reiterated the importance of ensuring all patients in the US can receive Treanda no matter what health care setting they go to. Teva raised concern about HCP's being offered an alternative to liquid might confuse people about whether to use lyophilized or liquid formulations.

FDA reinforced importance that Teva's DHCP letter and USPI labeling need to be very clear establishing consistent packaging with the PI/DHCP letter regarding availability to meet two different circumstances. Teva needs to anticipate a decrease in supply, and notify the FDA in advance.

FDA discussed concerns regarding a potential drug shortage with the lyophilized powder and if Teva has found any CSTD's that is compatible with N, N-Dimethylacetamide, and identifying treatment centers without a biosafety cabinet. Teva is currently searching for CSTD alternatives that are compatible with Treanda. Teva also asking the Agency if they develop a CSTD compatible with DMA could Treanda Lyophilized powder.

FDA is recommending for any future inquiries or complaints Teva receives, to gather more significant information on the event that occurred, and provide adequate access 24/7 available to HCP's.

FDA requesting Teva to submit all complaints or events should be reported to the Agency, and not wait weeks or months before we receive the information.

3.0 ACTION ITEMS:

Plan: Agency to do the following:

1. OCOMM: notify once USPI label and DHCP letter have been reviewed and approved.

Sponsor is to complete the following:

1. Sponsor must provide the compatibility information for syringes, and what's compatible with Treanda liquid. Complete further compatibility studies with CSTD's by COB, **Wednesday March 4, 2015**.

Complete by Tuesday, **March 3, 2015 at 10:00am:**

2. DHCP letter to provide clear options to avoid the problems encountered since marketing of the liquid solution formulation.
3. USPI labeling: recommend Teva add lyophilized powder information back into the prescribing information.
4. Update Carton-Container Labels

QUESTION :

Provide data to support the compatibility of BD polypropylene syringes with the Treanda liquid product.

COMPATIBILITY OF BD POLYPROPYLENE(PP) SYRINGES WITH TREANDA LIQUID

INTRODUCTION

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). Compatibility was determined via the following testing: appearance, organic impurities, and particulate matter. The composition of the Treanda liquid formulation is provided in [Table 1](#) for reference.

Table 1: Composition of the 45 mg/0.5 mL and 180 mg/2.0 mL Bendamustine Solution

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

1. MATERIALS AND METHODS

1.1. Materials

Treanda liquid: Baxter lot 3D005 (180 mg/2 mL vial)

Treanda liquid Placebo: lot RYL3708-170

BD 5 mL syringe: Ref # 309646 lot # 308637108 Material: Polypropylene

BD Needles: 18 gauge Precisionglide Ref # 305195 lot # 3117465

Amber screw cap vials: (b) (4) 40 mL, (b) (4)

Amber HPLC vials: (b) (4) lot # 13287333

1.2. Methods

1.2.1. Study Design

The bendamustine HCl in the Treanda drug product can cause interference with currently available analytical methods used to detect leachable substances from the polypropylene syringes. As a result, testing for leachables with the active drug product present in the samples would make it difficult to distinguish between solutes in the product and potential leachables from the syringe. To eliminate the potential for interference, the majority of the compatibility work was conducted with the placebo of the drug product which contained only DMA and propylene glycol.

A 5 mL sample of Treanda drug product or placebo was filled into into 5 mL polypropylene syringes. The syringes were labeled with appropriate identification, stored on a lab bench at ambient room temperature, and tested according to the protocol presented in [Table 2](#).

Table 2: Syringe Compatibility Testing Protocol

	Control ¹	Time 0 ²	5 min	15 min	30 min	60 min	120 min
Treanda	X	X	-	-	-	-	X
Placebo	XY	X	X	X	X	X	XY

1 Sample not exposed to syringe (bulk solution)

2 Prepare syringe with solution and immediately remove solution from the syringe

X = Appearance, Y = organic impurities

Particulate matter, USP<788> testing was also preformed by transferring Treanda liquid 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). Samples were tested according to the protocol presented in [Table 3](#).

1.11.1 Response to FDA Request for Information - Quality

Table 3: Syringe Compatibility Particulate Matter Testing Protocol

	Time 0¹	120 min
Treanda sodium chloride	X	X
Treanda dextrose/sodium chloride	X	X

1 Prepare syringe with solution and immediately remove solution from the syringe
X = Particulate matter, USP<788>

1.2.2. Analytical Procedures

1.2.2.1. Appearance (visual inspection)

Filled syringes are inspected visually for any cloudiness or visible particles in the solution. Syringes are also inspected for any abnormalities. All syringes are inspected versus a control sample.

1.2.2.2. Organic impurities by LC-MS

The LC/MS analysis was conducted with a Waters Acquity UPLC and Waters Synapt G2 high resolution mass spectrometer.

Operating Conditions:

Column : BEH C18 column (2.1x100 mm, 1.7 µm)
Column temperature : 35 °C
Mobile phase : Water/1% formic acid (A) and acetonitrile/1% formic acid (B)
Gradient : 20 minute gradient from 2% B to 100% B
Detection : MS: Electrospray source in positive ion mode and leucine enkephalin lockmass.
Compounds were also detected with an in-line PDA detector scanning from 210-450 nm
Injection volume : 5 µL

1.2.2.3. Organic impurities by GC-MS

A generic direct injection gas chromatography (GC) with MS detection method was used to determine volatile and semi-volatile organic compounds.

1.11.1 Response to FDA Request for Information - Quality

Operating Conditions:

Column	:	DB-5, 30m x 0.250mm, 0.25µm film thickness
Injection /detection temperature	:	250 °C/300 °C
Oven Program	:	40 °C, 2 min. – 15 °C/min. 300 °C
Detection	:	MS detection using positive polarity electron impact (EI+) ionization
Injection volume	:	1µL, splitless

1.2.2.4. Particulate matter, USP <788>

Particulate matter testing was performed at each required time point (n=3) as per USP <788>, method 1.A.

2. RESULTS

2.1. Syringe Compatibility Study

2.1.1. Appearance

Appearance was noted and recorded as per the protocol (Table 2) and the results are presented in Table 4. 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.

Table 4: Appearance Results

Sample	Control ¹	Time 0 ²	5 min	15 min	30 min	60 min	120 min
Treanda							
Solution	Clear, colorless to yellow liquid, no visible particles	No Change	---	---	---	---	No Change
Syringe	No abnormalities	No Change	---	---	---	---	No Change
Placebo							
Solution	Clear, colorless liquid, no visible particles	No Change	No Change	No Change	No Change	No Change	No Change
Syringe	No abnormalities	No Change	No Change	No Change	No Change	No Change	No Change

1 Sample not exposed to syringe (bulk solution)

2 Prepare syringe with solution and immediately remove solution from the syringe

2.1.2. Organic Impurities by Liquid Chromatography-Mass Spectrometry (LC-MS)

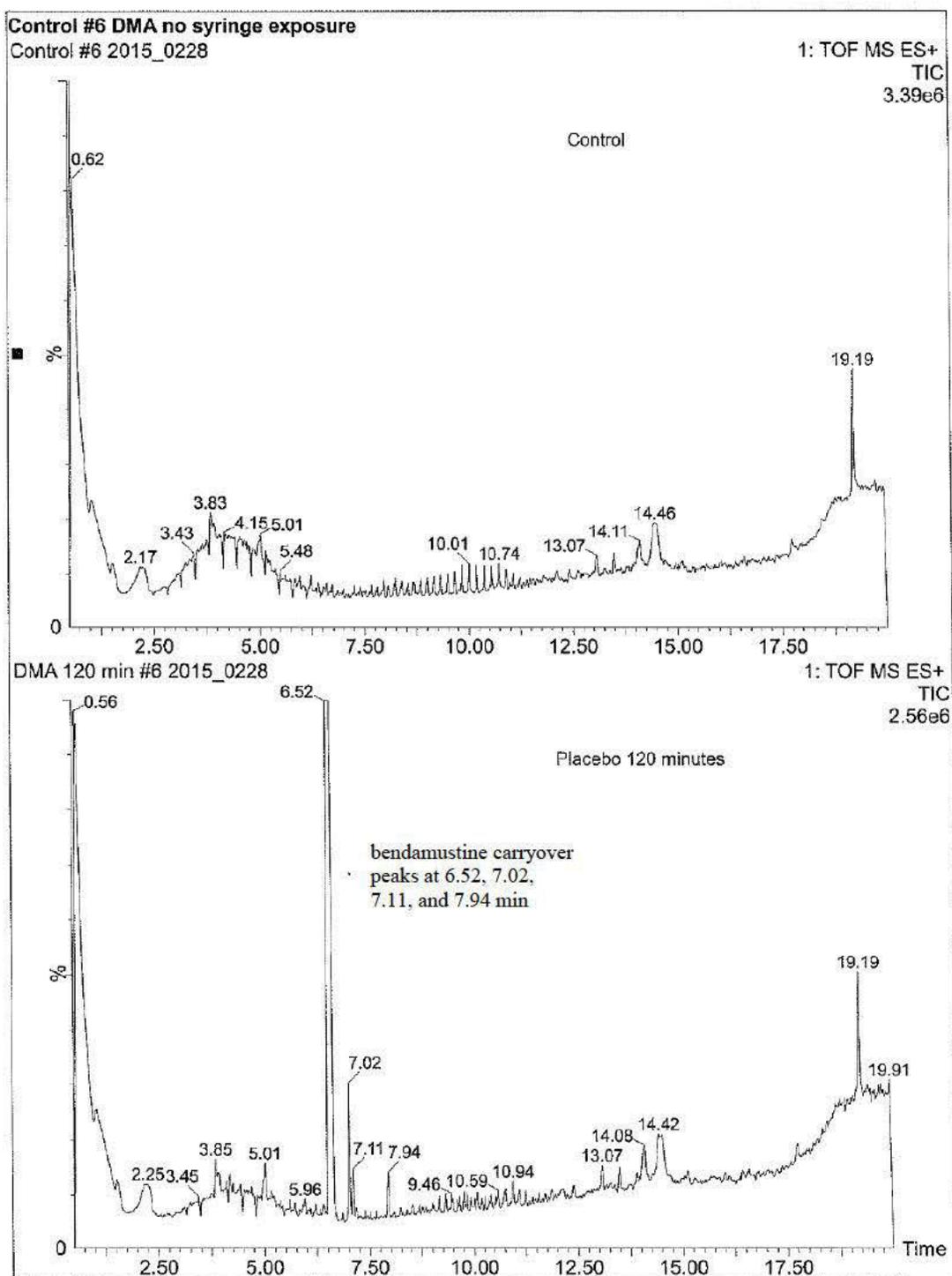
A comparison of the total ion chromatograms (TIC) of the control sample versus the placebo samples that were stored in polypropylene syringes for 120 minutes showed no new peaks. The results appear in [Table 5](#). A representative chromatogram of the control and 120 minute placebo sample which illustrates that no additional peaks were observed is presented in [Figure 1](#). The peaks at 6.52, 7.02, 7.11, and 7.94 minutes in the placebo chromatogram are due to carryover of bendamustine and related compounds based on their presence in the Treanda liquid control, mass spectra, and UV spectra. This carryover is due to a previous injection of the Treanda liquid control. A chromatogram of the Treanda liquid control demonstrating the interference which makes it difficult to distinguish between solutes in the product and potential leachables from the syringe is presented in [Figure 2](#).

Table 5: Organic Impurities by LC-MS Results

Sample	Control ¹	120 min
Placebo	See Figure 1	Comparable to control
Treanda	See Figure 2	Not tested due to interference from bendamustine seen in control

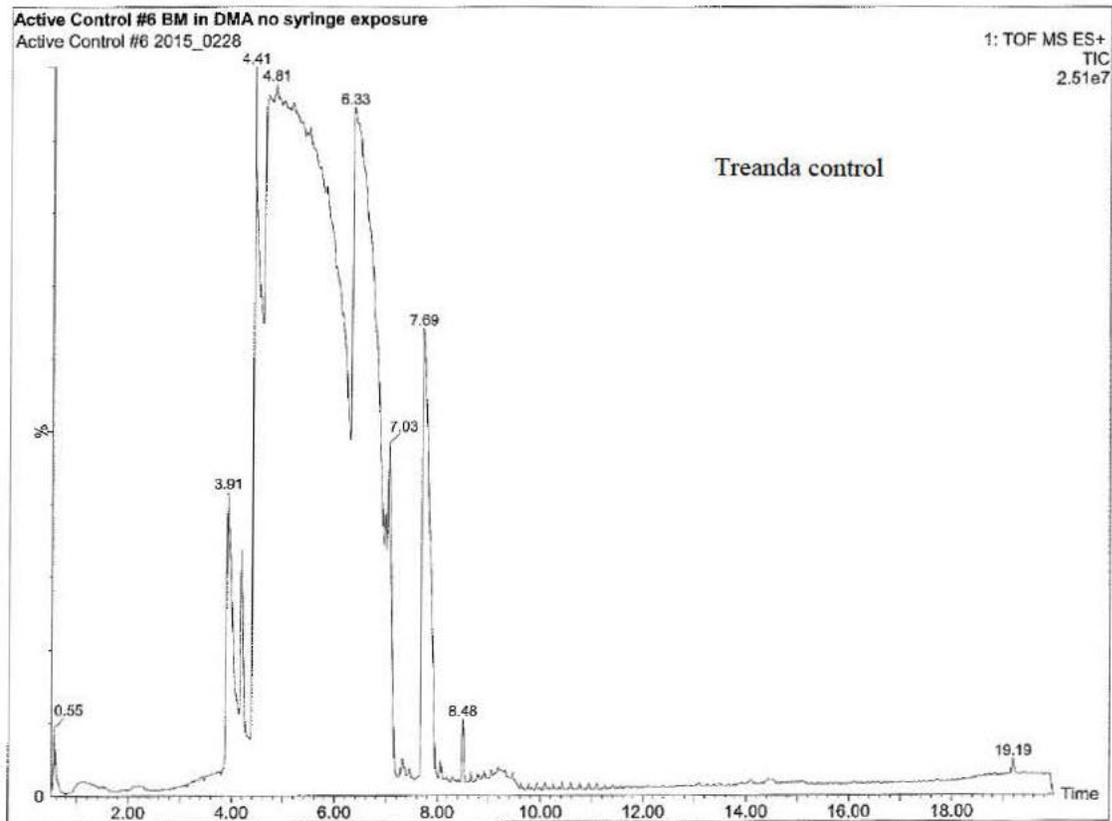
1 Sample not exposed to syringe (bulk solution)

Figure 1: Representative LC-MS Chromatogram of Control vs. Placebo



1.11.1 Response to FDA Request for Information - Quality

Figure 2: Representative LC-MS Chromatogram of Treanda



1.11.1 Response to FDA Request for Information - Quality

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

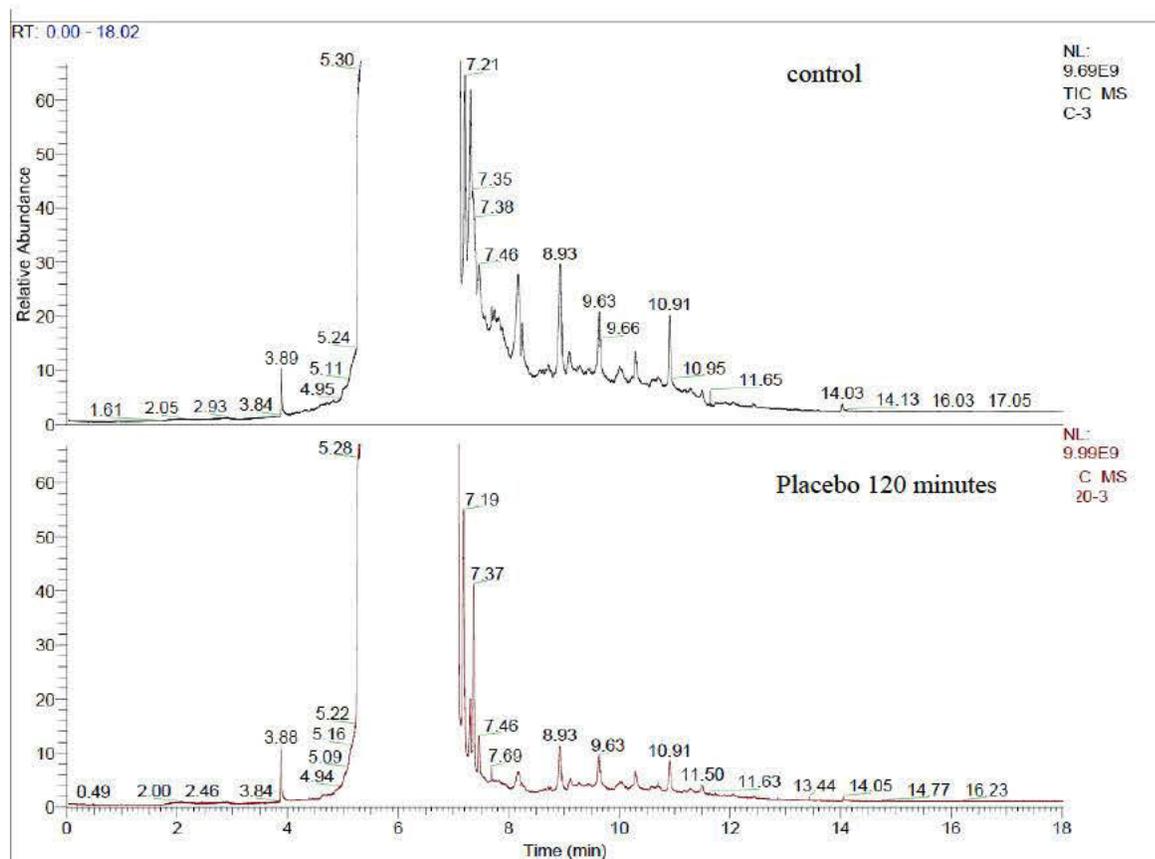
GC-MS analysis of volatile and semi-volatile analytes in samples of placebo that were stored in polypropylene syringes for 120 minutes yielded no peaks observed that were not in the control. The results appear in Table 6. A representative chromatogram of the control and 120 minute placebo sample which illustrates that no additional peaks were observed is presented in Figure 3.

Table 6: 3.1.3. Organic Impurities by GC-MS Results

Sample	Control ¹	120 min
Placebo	See Figure 3	Comparable to control

1 Sample not exposed to syringe (bulk solution)

Figure 3: Representative GC-MS Chromatogram of Control vs. Placebo



1.11.1 Response to FDA Request for Information - Quality

2.1.4. Particulate matter, USP <788>

Particulate matter testing was performed at each required time point in 3 bags for each diluent (n=3) as per the protocol (Table 3). The results presented in Table 7 are all acceptable and demonstrate that no solublized extracts from the polypropylene syringes have precipitated in the infusion bags.

Table 7: Particulate Matter Results

Sample	Bag #	Treanda in 0.9% sodium chloride		Treanda in 2.5% dextrose/0.45% sodium chloride	
		Average (n=3) Particles >10 um	Average(n=3) Particles >25 um	Average (n=3) Particles >10 um	Average (n=3) Particles >25 um
T₀					
	1	6	1	3	0
	2	3	0	3	0
	3	6	0	2	0
120 minutes					
	1	4	0	4	0
	2	3	0	2	0
	3	4	0	5	1

2.2. 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 directly correlated to the 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.

2.2.1. Chemical Stability

Treanda liquid drug product was aseptically withdrawn from the glass vials using a polypropylene syringe (3 mL BD reference 309657, 5 mL BD reference 309646, 10 mL BD reference 309604) and immediately transferred into the IV bag. Data from the study for the admixture solution at 0.2 mg/mL in 0.9% Sodium Chloride, USP solution stored at 5 °C and 25 °C/60%RH are presented in [Table 8](#) and [Table 9](#), respectively. Data from the admixture solution at 0.7 mg/mL in 0.9% Sodium Chloride, USP solution stored at 5 °C and 25 °C/60%RH are presented in [Table 10](#), and [Table 11](#), respectively.

Table 8: Results for Bendamustine Solution in 0.9% Sodium Chloride Admixture at 5 °C (0.2 mg/mL)

Test	Timepoint (hours)					
	Initial	2	4	8	12	24
Assay (% initial concentration)	100	99	99	99	98	97
Degradation products (%)						
RRT 0.55	ND	ND	ND	ND	ND	ND
CEP-43717	0.1	0.1	0.1	0.1	0.1	0.1
CEP-43714	0.1	0.8	1.1	1.6	1.9	3.0
CEP-43713	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
CEP-43658	0.6	0.6	0.6	0.6	0.6	0.6
CEP-43659	0.1	0.1	0.1	0.1	0.1	0.1
CEP-43716	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.1
CEP-43712	0.1	0.1	0.1	0.1	0.1	0.1
Total degradation products (%)	1.1	1.8	2.0	2.5	2.9	4.0

ND = None Detected LOQ = Limit of Quantitation = 0.05%

1.11.1 Response to FDA Request for Information - Quality

Table 9: Results for Bendamustine Solution 0.9% Sodium Chloride Admixture at 25 °C/60% RH (0.2 mg/mL)

Test	Timepoint (hours)		
	Initial	2	3
Assay (% initial concentration)	100	97	95
Degradation products (%)			
RRT 0.55	ND	ND	< LOQ
CEP-43717	0.1	0.1	0.1
CEP-43714	0.2	2.9	4.5
CEP-43713	< LOQ	< LOQ	< LOQ
CEP-43658	0.6	0.6	0.6
CEP-43659	0.1	0.1	0.1
CEP-43716	< LOQ	< LOQ	0.1
CEP-43712	0.1	0.1	0.1
Total degradation products (%)	1.2	3.9	5.5

ND = None Detected LOQ = Limit of Quantitation = 0.05%

Table 10: Results for Bendamustine Solution in 0.9% Sodium Chloride Admixture at 5 °C (0.7 mg/mL)

Test	Timepoint (hours)					
	Initial	2	4	8	12	24
Assay (% initial concentration)	100	100	99	99	99	98
Degradation products (%)						
RRT 0.55	ND	ND	ND	ND	ND	ND
CEP-43717	< LOQ	0.1	< LOQ	< LOQ	< LOQ	< LOQ
CEP-43714	0.2	0.8	1.1	1.5	1.8	2.8
CEP-43713	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
CEP-43658	0.6	0.6	0.6	0.6	0.6	0.6
CEP-43659	0.1	0.1	0.1	0.1	0.1	0.1
CEP-43716	< LOQ	< LOQ	< LOQ	0.1	0.1	0.1
CEP-43712	0.1	0.1	0.1	0.1	0.1	0.1
Total degradation products (%)	1.1	1.7	2.0	2.4	2.8	3.8

ND = None Detected LOQ = Limit of Quantitation = 0.05%

1.11.1 Response to FDA Request for Information - Quality

Table 11: Results for Bendamustine Solution 0.9% Sodium Chloride Admixture at 25 °C/60% RH (0.7 mg/mL)

Test	Timepoint (hours)		
	Initial	2	3
Assay (% initial concentration)	100	99	97
Degradation products (%)			
RRT 0.55	ND	ND	< LOQ
CEP-43717	< LOQ	< LOQ	< LOQ
CEP-43714	0.2	2.5	3.9
CEP-43713	< LOQ	< LOQ	< LOQ
CEP-43658	0.6	0.6	0.6
CEP-43659	0.1	0.1	0.1
CEP-43716	< LOQ	0.1	0.1
CEP-43712	0.1	0.1	0.1
Total degradation products (%)	1.1	3.5	4.9

ND = None Detected LOQ = Limit of Quantitation = 0.05%

Data from the admixture solution at 0.2 mg/mL in 2.5% Dextrose/0.45% Sodium Chloride, USP solution stored at 5 °C and 25 °C/60%RH are presented in [Table 12](#) and [Table 13](#), respectively. Data from the admixture solution at 0.7 mg/mL in 2.5% Dextrose/0.45% Sodium Chloride, USP solution stored at 5 °C and 25 °C/60%RH are presented in [Table 14](#) and [Table 15](#), respectively.

1.11.1 Response to FDA Request for Information - Quality

Table 12: Results for Bendamustine Solution in 2.5% Dextrose/0.45% Sodium Chloride Admixture at 5 °C (0.2 mg/mL)

Test	Timepoint (hours)					
	Initial	2	4	8	12	24
Assay (% initial concentration)	100	99	99	98	98	96
Degradation products (%)						
RRT 0.55	ND	ND	ND	ND	ND	< LOQ
RRT 0.77	0.1	0.1	0.1	0.3	ND	0.2
CEP-43717	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
CEP-43714	0.2	1.0	1.4	1.9	2.4	3.8
CEP-43713	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
CEP-43658	0.6	0.6	0.6	0.6	0.6	0.6
CEP-43659	0.1	0.1	0.1	0.1	0.1	0.1
CEP-43716	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.1
CEP-43712	0.1	0.1	0.1	0.1	0.1	0.1
Total degradation products (%)	1.1	1.9	2.3	3.0	3.3	4.9

ND = None Detected LOQ = Limit of Quantitation = 0.05%

Table 13: Results for Bendamustine Solution in 2.5% Dextrose/0.45% Sodium Chloride Admixture at 25 °C/60% RH (0.2 mg/mL)

Test	Timepoint (hours)		
	Initial	2	3
Assay (% initial concentration)	100	97	95
Degradation products (%)			
RRT 0.55	ND	< LOQ	0.1
RRT 0.77	0.2	0.4	0.3
CEP-43717	< LOQ	< LOQ	< LOQ
CEP-43714	0.2	3.6	5.6
CEP-43713	< LOQ	< LOQ	< LOQ
CEP-43658	0.6	0.6	0.6
CEP-43659	0.1	0.1	0.1
CEP-43716	< LOQ	< LOQ	0.1
CEP-43712	0.1	0.1	0.1

ND = None Detected LOQ = Limit of Quantitation = 0.05%

1.11.1 Response to FDA Request for Information - Quality

Table 14: Results for Bendamustine Solution in 2.5% Dextrose/0.45% Sodium Chloride Admixture at 5 °C (0.7 mg/mL)

Test	Timepoint (hours)					
	Initial	2	4	8	12	24
Assay (% initial concentration)	100	100	99	99	99	98
Degradation products (%)						
RRT 0.55	ND	ND	ND	ND	ND	ND
RRT 0.77	ND	< LOQ	0.1	< LOQ	ND	ND
CEP-43717	< LOQ	0.1	< LOQ	< LOQ	< LOQ	< LOQ
CEP-43714	0.6	1.1	1.4	1.8	2.3	3.8
CEP-43713	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
CEP-43658	0.6	0.6	0.6	0.6	0.6	0.6
CEP-43659	0.1	0.1	0.1	0.1	0.1	0.1
CEP-43716	< LOQ	< LOQ	< LOQ	0.1	0.1	0.1
CEP-43712	0.1	0.1	0.1	0.1	0.1	0.1
Total degradation products (%)	1.5	2.0	2.3	2.7	3.2	4.8

ND = None Detected LOQ = Limit of Quantitation = 0.05%

Table 15: Results for Bendamustine Solution in 2.5% Dextrose/0.45% Sodium Chloride Admixture at 25 °C/60% RH (0.7 mg/mL)

Test	Timepoint (hours)		
	Initial	2	3
Assay (% initial concentration)	100	97	95
Degradation products (%)			
RRT 0.55	ND	< LOQ	0.1
RRT 0.77	ND	0.1	ND
CEP-43717	< LOQ	< LOQ	< LOQ
CEP-43714	0.3	3.4	5.2
CEP-43713	< LOQ	< LOQ	< LOQ
CEP-43658	0.6	0.6	0.6
CEP-43659	0.1	0.1	0.1
CEP-43716	< LOQ	0.1	0.1
CEP-43712	0.1	0.1	0.1
Total degradation products (%)	1.2	4.3	6.2

ND = None Detected LOQ = Limit of Quantitation = 0.05%

1.11.1 Response to FDA Request for Information - Quality

2.2.2. 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 results are summarized in [Table 16](#). The diluted solutions were colorless and free from particulate matter (with no change in particulate matter) under the conditions utilized for the study.

Table 16: Particulate Matter Testing

Diluent	Bendamustion concentration (mg/mL)	Average Particles 10 µm	Average Particles 25 µm
0.9% Sodium chloride	Blank	1	0
0.9% Sodium chloride	0.7 mg/mL	2	0
0.9% Sodium chloride	0.2 mg/mL	6	0
2.5% Dextrose/0.45% Sodium chloride	Blank	0	0
2.5% Dextrose/0.45% Sodium chloride	0.7 mg/mL	1	0
2.5% Dextrose/0.45% Sodium chloride	0.2 mg/mL	5	0

These studies further support the compatibility of the Treanda liquid formulation with polypropylene syringes.

3. 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 BD polypropylene syringes with metal needles has been demonstrated. No differences were noted between the control samples and placebo samples stored in the BD polypropylene syringes for 120 minutes. Samples of Treanda liquid stored in the BD polypropylene syringes for up to 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 BD polypropylene syringes with metal needles be used to transfer Treanda liquid from the vial to the IV bags.

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/s/

KIMBERLY L SCOTT
04/01/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: February 27, 2015
Time: 3:00 PM – 3:45 PM

Application Number: NDA 022249

Product Name: Treanda (Bendamustine HCL)

Applicant Name: TEVA (Cephalon wholly owned subsidiary of TEVA Pharmaceuticals)

Subject: Agency requested a teleconference with Teva to discuss safety concerns and potential recall of the liquid formulation of the product.

FDA Participants:

Office of Hematology and Oncology Products(OHOP)

Richard Pazur, MD, Office Director
Paul Kluetz, MD, Acting Deputy Director
Tamy Kim, PharmD, Associate Director of Regulatory Affairs

OHOP/Division of Hematology Products

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Theresa Carioti, MPH, Chief Project Management Staff
Kimberly Scott, RN, BSN, OCN, Regulatory Project Manager

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Sue Ching Lin, PhD, CMC Reviewer

Office of Surveillance and Epidemiology, Division of Medication Errors and Prevention

Jo Wyeth, Safety Evaluator
Yelena Maslov, PharmD, Team Leader

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Catherine Gould, RPh, Branch Chief

OC/Division of Drug Quality II/Office of Manufacturing Quality/ Global Compliance Branch IV
Jay Jariwala, Consumer Safety Officer
Leo Zadecky, RPh, Senior Program Manager

OC/ Prescription Drugs Branch/Office of Unapproved Drugs and Labeling Compliance
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Office of Communications
Paula Rausch PhD, RN, Director
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Sponsor Participants

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Dennis Ahern, Sr. Director, Regulatory Affairs
Nina Moore, Manager, Regulatory Affairs
Sylvie Peltier, Sr. Director, Regulatory Affairs, CMC
Shirley Speer, Sr. Manager, Regulatory Affairs, CMC
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Marazban Sarkari, Associate Director, Pharmaceutical Development
Andrea Pless, Associate Director, Validation and QC
Donald Hora, Sr. Manager, Global Labeling
Joseph DeVito, VP, Validation and QC Validation
Leonard James, Director, Pharmacovigilance
Donald Gee, Associate Director, Global Quality Compliance
Robin Jones, VP, Quality Compliance

1.0 BACKGROUND:

The liquid formulation of Treanda was approved on September 13, 2015. Prior to the marketing of the liquid formulation, there was a lyophilized powder formulation, which was the initial product formulation, approved in 2008.

On February 12, 2015, Division of Drug Information received a complaint from a hospital pharmacist that described a problem with Treanda liquid solution, melting of the syringe adaptor hub that caused the Treanda to leak out. A photo of the melted Tevadaptor was also included.

The pharmacist noted that the new formulation contains the (b) (4) N, N-dimethylacetamide and that this (b) (4) is not compatible with devices containing polycarbonate.

Teva contacted the Division on February 13, 2015 with a proposed Dear Healthcare Provider letter (DHCP) to describe the risks associated with using close system transfer device with products that contain N, N-Dimethylacetamide.

The Division met internally on February 25, 2015 to discuss the safety issues for Treanda liquid formulation and the next steps for advising the applicant to incorporate necessary labeling changes. The Agency has learned through follow-up information request to Teva that there have been several reported complaints (at least 45 since December 9, 2014) with the liquid Treanda product and closed system transfer devices; including leaking, melting of the syringe/adaptor hub, cloudy product in bag, etc.

At present, there are safety concerns with the compatibility of the liquid product with devices, including closed system transfer devices, syringes, IV catheters, IV bags, gloves, etc. The Division is recommending Teva change their USPI label and issue DHCP letter.

Teva is to respond to an information request, outlining what the drug is compatible with by February 27, 2015 at 2:00pm. The Division wants to issue an official safety communication, and potentially recall the liquid formulation of the product.

Office of Communications (OCOMM) has been informed of the safety issues and the need to prepare an FDA CDER statement. T CDRH's general health hospital device branch (GHDB) was also consulted for their input on the devices used with Treanda liquid.

Teva was unable to provide compatibility information for Treanda liquid formulation by the requested February 27, 2015. Teva is to submit some compatibility studies by Monday, March 2, 2015 at 8:30am.

2.0 DISCUSSION:

The FDA expressed their concern with Teva's lack of response for informing the Agency sooner of the reported complaints associated with leaking of Treanda liquid formulation when used with Closed System Transfer Devices (CSTDs). Since December 9, 2014, the various complaints have included leaking and melting to the syringe, breaking and operation failures of the CSTD, cloudy appearance or presence of particulate matter in the IV bag after dilution.

The FDA stated the potential safety concerns for health care provider's safety and the potential harm Treanda liquid solution could cause with certain types of gloves, IV Bags, solutions, IV catheters, etc. The FDA asked Teva what their plans are regarding identification of which plastics are compatible with Treanda liquid. Teva responded they have a list of products that Treanda is compatible with. The Agency stated the importance for Teva to disseminate the DHCP letter to the public as soon as possible. Teva acknowledged the urgency and stated their intent to work with the Agency to gain agreement on the proposed language for the letter.

Teva stated the primary concern associated with the complaints is with the use of CSTD's. Teva also reported that BD polypropylene syringes are compatible with Treanda.

FDA also discussed possibility of suspending Treanda Injection from the market. FDA explained that would not be the preferred route; however, if Teva does not respond appropriately, that action would be considered. The Agency noted they will await Teva's response on Monday,

March 2, 2015 by 8:30am to provide labeling changes to the Prescribing Information and edits to the Dear Healthcare Provider letter. Teva acknowledged the Agency's request and agreed to submit the requested changes by the provided date and time.

FDA inquired about the available supply status for both formulations of Treanda, liquid and lyophilized powder. Teva responded stating they are unsure of the exact amount, but sent information (see attached) in response to the information request.

FDA reiterated the need for Teva to revise the DHCP letter and ensure the information is consistent with the information in the PI. To address compatibility concerns, FDA advised Teva to consider what other devices could potentially come in contact with the Treanda liquid drug product, before and during administration, and following infusion. This includes syringes, CSTDs, gloves, IV tubing/bags, IV catheters, etc. In addition, FDA advised Teva to not only reference TevAdapter in their proposed DHCP letter, but rather broaden the scope of the message that Treanda liquid solution should **not** be used with materials that contain polycarbonate.

FDA further recommended if Teva continues to market the lyophilized formulation, they will need to revise the prescribing information to include adequate information in the labeling for lyophilized formulation. Based on their current information to avoid potential drug shortage with Treanda, it appears it will be necessary to keep the lyophilized formulation.

3.0 ACTION ITEMS:

Plan: Agency to do the following:

1. Schedule Sponsor meeting for Monday, March 2, 2015 at 12:00PM.

Sponsor is to complete the following by Monday, March 2, 2015 at 8:30am:

1. Provide Teleconference number for meeting at 12:00pm, Monday, March 2, 2015.
2. DCHP letter
 - a. Needs major editing to encompass the scope of the problem.
 - b. Provides a safe alternative procedure for all methods of preparation.
 - c. Provide edits or comments to the attached label with track changes.
3. PI Label:
 - a. Provide edits or comments to the attached label with track changes.
 - b. Treanda and Lyophilized Powder to be combined into one label.
 - c. Revise section 2.3
 - d. Needs to include polycarbonate not compatible, but note what devices are compatible (gloves, syringes, etc.)
4. Submit Compatibility studies with polycarbonate using Treanda Liquid.
5. Provide a plan for those health care providers and pharmacies that do not have Closed System Transfer Devices, and what safety issues will be put in place to assure no problems with melting/leaking.

FDA QUESTION 1:

Please comment on the availability of both the liquid and lyophilized powder formulations of TREANDA. Furthermore, what is the supply and distribution status of the lyophilized product?

Sponsor’s Response

Table 1 represents the current available inventory and distribution status of the TREANDA liquid and lyophilized powder formulations.

Table 1: TREANDA Current Inventory

		At US Warehouse		At Production Sites		Total	
		In Vials	In Months	In Vials	In Months	In Vials	In Months
Treanda Lyo	25mg	(b) (4)					
	100mg						
Treanda LQ	45mg						
	180mg						

a

(b) (4)

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/s/

KIMBERLY L SCOTT
04/01/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: February 27, 2015
Time: 9:15am - 10:00am

Application Number: NDA 022249

Product Name: Treanda (Bendamustine HCL)

Applicant Name: TEVA (Cephalon wholly owned subsidiary of TEVA Pharmaceuticals)

Subject: Treanda's in-compatibility with Closed System Transfer Devices containing polycarbonate

FDA Participants:

Division of Hematology Products

Angelo de Claro, MD, Clinical Team Leader
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Qin Ryan, MD, Safety Medical Officer
Robert Kane, MD, Deputy Director of Safety
Diane Leaman, Safety Project Manager
Theresa Carioti, MPH, Chief Project Management Staff
Kimberly Scott, RN, BSN, OCN, Regulatory Project Manager

Office of Pharmaceutical Science, Office of Lifecycle Drug Products

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Sue Ching Lin, PhD, CMC Reviewer

Office of Surveillance and Epidemiology, Division of Medication Errors and Prevention

Jo Wyeth, Safety Evaluator
Yelena Maslov, PharmD, Team Leader

OC/Division of Drug Quality II/Office of Manufacturing Quality/ Global Compliance Branch IV

Jay Jariwala, Consumer Safety Officer
Leo Zadecky, RPh, Senior Program Manager

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Catherine Gould, RPh, Branch Chief

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Aaron Weisbuch, JD, Regulatory Status and Labeling Team

Lesly Frank, PhD, JD, Regulatory Counsel
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Robin Jones, VP Quality Compliance
Joe DeVito, Associate Director, Validation and QC Validation
Leonard James, M.D., Director, Pharmacovigilance
Donald Gee, Associate Director, Global Quality Compliance

1.0 BACKGROUND:

The liquid formulation of Treanda was approved on September 13, 2015. Prior to the marketing of the liquid formulation, there was a lyophilized powder formulation, which was the initial product formulation, approved in 2008.

On February 12, 2015, Division of Drug Information received a complaint from a hospital pharmacist that described a problem with Treanda liquid solution, melting of the syringe adaptor hub that caused the Treanda to leak out. A photo of the melted Tevadaptor was also included.

The pharmacist noted that the new formulation contains the (b)(4) N, N-dimethylacetamide and that this (b)(4) is not compatible with devices containing polycarbonate.

Teva contacted the Division on February 13, 2015 with a proposed Dear Healthcare Provider letter (DHCP) to describe the risks associated with using close system transfer device with products that contain N, N-Dimethylacetamide.

The Division met internally on February 25, 2015 to discuss the safety issues for Treanda liquid formulation and the next steps for advising the applicant to incorporate necessary labeling changes. The Agency has learned through follow-up information request to Teva that there have been several reported complaints (at least 45 since December 9, 2014) with the liquid Treanda product and closed system transfer devices; including leaking, melting of the syringe/adaptor hub, cloudy product in bag, etc.

2.0 DISCUSSION:

The FDA stated they had received numerous complaints related to the leaking of Treanda Liquid formulation with Closed System Transfer Devices (CSTD), which causes leaking and melting to

the syringe, breaking and operation failures of the CSTD, cloudy appearance or presence of particulate matter in the IV bag after dilution since December 9, 2014.

The FDA further discussed the potential safety concerns for health care provider's safety, and the potential harm Treanda liquid solution could cause with certain types of gloves, IV Bags, solutions, IV catheters, etc.

The FDA specifically advised Teva to consult with CDRH regarding subsequent actions and follow-up with specific devices. Teva responded that they've consulted with CDRH, and are waiting to find out their evaluations, but specifically, Teva indicated that CDRH is not mandating any reports at this time.

FDA also discussed submitting the necessary labeling changes as a CBE 0 supplement. FDA discussed labeling changes to the Prescribing Information and edits to the Dear Healthcare Provider letter. Teva acknowledged and agreed to the plan to submit the revised labeling as a CBE-0 supplement within one week, by Friday, March 6, 2015. Teva also indicated they want to have the DHCP letter sent out ASAP, once they have agreement with the Agency on the language.

The clinical division explained the importance of working with the Agency to gain agreement on the content of the DHCP letter to avoid having to reissue the letter.

Teva clarified the Agency's request for compatibility data and the FDA confirmed that they are requesting preliminary data with gloves, tubing, and catheter.

FDA reiterated the need for Teva to revise the DHCP letter and ensure the information is consistent with the information in the PI. In addition, Teva will need to make reference to those syringes or CSTD's (might include gloves) that do not contain polycarbonate. FDA questioned if Teva was aware of incompatibility with the use of certain gloves and Teva's product quality representative responded saying they have identified some gloves are not compatible with handling Treanda.

FDA suggested Teva to further discuss internally how they're going to make changes to the USPI. They will need to follow up with data to support their changes.

3.0 ACTION ITEMS:

Plan: Agency to do the following:

1. Contact OCOMM – the need for safety communication
2. Consult CDRH
 - a. Suggest changes to the Prescribing Information and DHCP letter are to be reviewed and recommendations or suggestions, if needed.
3. OSE, DMEPA, Safety agree the DHCP letter and labeling changes need to be done regarding section 2.3.

Sponsor is to complete the following:

1. send proposed changes to DHCP letter and PI Label:

- a. Needs to state liquid solution is not compatible with polycarbonate; and also note what devices Treanda liquid is compatible with, i.e. gloves, syringes, etc.
2. Comment on the availability of both the liquid and lyophilized powder formulations of Treanda, specifically FDA requests the supply and distribution status of the lyophilized product

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

/s/

KIMBERLY L SCOTT
03/23/2015

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: March 10, 2015
Requesting Office or Division: Division of Hematology Products
Application Type and Number: NDA 22249/S-19
Product Name and Strength: Treanda (Bendamustine Hydrochloride) Injection,
45 mg /0.5 mL and 180 mg/2 mL (90 mg/mL)
Submission Date: March 6, 2015 and March 9, 2015
Applicant/Sponsor Name: Teva
OSE RCM #: 2015-355
DMEPA's Review Author/Team Leader: Yelena Maslov, Pharm.D

1 PURPOSE OF MEMO

Division of Hematology Products (DHP) requested that we review container label and carton labeling to determine if they are acceptable from a medication error perspective. Additionally, DHP requested we provide Teva with naming options for their bendamustine injection to help prevent medication errors related to confusion between the two formulations of bendamustine hydrochloride due to different products' concentrations. DHP is requesting these recommendations due to the safety issue related to Treanda Injection. 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 vial labels and carton labeling and conclude that the labels and labeling can be improved to help prevent medication errors related to the wrong use of the product with incompatible devices.

Additionally, we provide recommendations regarding proprietary naming options in response to Division's request to consider product's name change due to possible confusion between the two dosage forms due to difference in concentrations between Treanda's lyophilized powdered and injection.

3 RECOMMENDATIONS TO TEVA

Until carton labeling and vial changes are implemented, as an interim measure for Treanda liquid product that has already been distributed to pharmacies, hospitals, etc., you need to provide stickers/labels that can adhere to the carton labeling with the Treanda liquid product. FDA recommends the following statement on the sticker: **"Not for use with devices that contain polycarbonate or acrylonitrile-butadiene-styrene (ABS)"**. The sticker should be accompanied with the DHCP letter. Furthermore, the same sticker should be attached to carton and any other appropriate labeling of already existing and ready for shipment product supply at the manufacturers and distributors sites.

Carton Labeling

1. In the proposed statement " Do not use with devices that contain polycarbonate or acrylonitrile butadiene-styrene (ABS)" increase the prominence of negation "NOT", by using all capital letters or bolding as negative sentences containing NOT can be misinterpreted as the opposite since NOT can be overlooked".
2. Increase the prominence of the storage information on the side panel by bolding the entire statement "Store refrigerated at...." As storage for Treanda Injection differs from the storage of Treanda for Injection and this information should be easily identified by healthcare providers.

Vial Container

1. We recommend addition of a flag to the actual vial containing a statement "Do not use with devices that contain polycarbonate or acrylonitrile butadiene-styrene (ABS)" on the container. Increase the prominence of negation "NOT", by using all capital letters or bolding as negative sentences containing NOT can be misinterpreted as the opposite since NOT can be overlooked.

Proprietary Name

To help prevent medication errors related to confusion between the two formulations of bendamustine hydrochloride due to different products' concentrations, we recommend you consider one of the following options regarding proprietary name:

1. Propose a modifier to be added to the proprietary name Treanda for the injection dosage form to help differentiate the product from the lyophilized powder formulation and submit to the Agency for evaluation. We continue to recommend against the use modifier "LQ" as stated in proprietary name request unacceptable letter sent to you on June 13, 2013 (see attached).
2. Alternatively, you can propose a dual proprietary name for the injection dosage form. However, if choosing this option, consider retaining a portion of the original Treanda name in the new name (e.g. TreanXXXX) so health care practitioners recognize that this product is associated with, (or an extension of) Treanda.

Please submit a request for review of your proposed proprietary name. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>).

Further information about how FDA evaluates propriety names for drug products is available in the following guidance, Best Practices in Developing Proprietary Names for Drugs (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)

Appendix A. Label and Labeling Submitted on INSERT DATE

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

/s/

YELENA L MASLOV
03/10/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 022249/S-19

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMC 1

NDA/BLA # NDA 22-249
Product Name: Treanda (bendamustine hydrochloride) Injection

PMC Description: Submit quarterly reports until March 2017 of complaints about preparation and use of Treanda Injection (solution) and Treanda for Injection (lyophilized powder).

PMC Schedule Milestones:

Final Protocol Submission:	N/A
Interim Report (March 1, 2015 through May 31, 2015):	June 2015
Interim Report (June 1, 2015 through August 31, 2015):	September 2015
Interim Report (September 1, 2015 through November 30, 2015):	December 2015
Interim Report (December 1, 2015 through February 29, 2016):	March 2016
Interim Report (March 1, 2016 through May 31, 2016):	June 2016
Interim Report (June 1, 2016 through August 31, 2016):	September 2016
Interim Report (September 1, 2016 through November 30, 2016):	December 2016
Interim Report (December 1, 2016 through February 28, 2017):	March 2017
Study Completion:	March 2017
Final Report Submission:	June 2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Due to the possibility of use of Treanda Injection (45mg/0.5 mL or 180 mg/2 mL solution) with additional devices, it is necessary to continue monitoring complaints regarding the use of various devices with Treanda Injection to determine if further action is necessary to address new adverse interactions that may be seen with products that come into contact with Treanda Injection. Treanda injection contains a (b) (4) that melts certain plastics such as certain types of needle hubs and drug transfer devices (see below).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The new formulation, Treanda Injection (45 mg/0.5 mL or 180 mg/2 mL solution) contains N,N-dimethylacetamide (DMA) which is incompatible with polycarbonate and acrylonitrile-butadiene-styrene (ABS). Closed system transfer devices (CSTDs), adaptors, and syringes containing polycarbonate or ABS have been shown to dissolve when they come into contact with DMA. This PMC is to monitor complaints with the use of Treanda Injection with various devices in a periodic reporting format.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Periodic summary of preparation complaints to applicant.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

DIANE V LEAMAN
08/21/2015

ROBERT C KANE
08/21/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, August 18, 2015 12:38 PM
To: Mike McGraw (Mike.McGraw@tevapharm.com)
Cc: Scott, Kimberly
Subject: NDA 022249 Treanda: FDA edits to USPI and DHCP letter
Attachments: NDA 22249 FDA edits Treanda Proposed DHCP letter .docx; NDA 22249 FDA Edits to Treanda Proposed Labeling Text - Tracked.doc

Importance: High

Dear Mike,

The Agency has made suggested edits to Teva's labeling supplement, NDA 22249 Treanda (see attached USPI and DHCP letter). Edits were made to the USPI to Section 6 regarding current labeling practices, but we have no edits related to the new content proposed in Section 2.

Per the Agency request, we look forward to receiving your proposed USPI and DHCP letter by Friday, August 21, 2015.

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

From: Mike McGraw [mailto:Mike.McGraw@tevapharm.com]
Sent: Monday, August 17, 2015 3:20 PM
To: Scott, Kimberly
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11

Dear Kimberly,

Thank you very much for meeting with us last week.

During the discussion, FDA stated that we may receive comments on our draft Dear Healthcare Provider letter and the draft USPI.

Can you confirm whether we will receive comments?

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, August 11, 2015 8:39 AM
To: Mike McGraw
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11
Importance: High

Dear Mike,

Thank you for providing the toll free number.

Thanks,
Kim

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Tuesday, August 11, 2015 8:02 AM
To: Scott, Kimberly
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11
Importance: High

Dear Kimberly,

For our teleconference today, I also want to provide a toll-free number:

 (b) (4)

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, August 10, 2015 1:25 PM
To: Mike McGraw
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11
Importance: High

Dear Mike,

The Agency is planning to discuss Teva's proposed plans for Treanda sent on July 24, 2015.

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

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]

Sent: Monday, August 10, 2015 12:05 PM

To: Scott, Kimberly

Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11

Dear Kimberly,

Our teleconference for Treanda is scheduled for tomorrow. Can you clarify if there are any specific issues within the proposals that the Agency would like to discuss?

Regards,

Mike



Michael J. McGraw Director, Regulatory Affairs

Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230

Mike.McGraw@tevapharm.com www.tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]

Sent: Friday, July 31, 2015 6:18 AM

To: Mike McGraw

Cc: Shirley Speer; Donald Hora Jr

Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11

Importance: High

Dear Mike,

Thank you for confirming Teva teams availability and providing the number for the teleconference Tuesday, August 11, 2015.

Regards,

Kimberly

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

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Thursday, July 30, 2015 10:47 PM
To: Scott, Kimberly
Cc: Shirley Speer; Donald Hora Jr
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11

Dear Kimberly,

The Teva team is available for a teleconference on August 11, 2015 from 9:15-10:00AM (ET).

Here is the phone number for the conference:

 (b) (4)

Please let me know if you have any questions.

Regards,
Mike

	Michael J. McGraw Director, Regulatory Affairs Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230 Mike.McGraw@tevapharm.com www.tevapharm.com
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From: Mike McGraw
Sent: Thursday, July 30, 2015 2:35 PM
To: 'Scott, Kimberly'
Cc: Shirley Speer; Donald Hora Jr
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11
Importance: High

Dear Kimberly,

I confirm receipt of your e-mail.

I will contact the Teva team and confirm availability as soon as possible.

Are there any specific issues within the proposals that the Agency would like to discuss?

Please note that I will be out of the office next week and beginning tomorrow. If you have any questions or issues during that time, please send them to my colleagues, Shirley Speer and Donald Hora (both copied here), and copy me.

Please let me know if you have any questions.

Regards,

Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, July 30, 2015 2:05 PM
To: Mike McGraw
Subject: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11
Importance: High

Good afternoon Mike,

The Agency is requesting Teva be available to discuss NDA 22249 Treanda via teleconference Tuesday, August 11, 2015 from 9:15AM – 10:00AM (ET). The Agency will be discussing the proposals Teva sent via email on Friday, July 24, 2015.

Please let me know if you and your team are available. If so, please provide a phone number for the conference.

Please acknowledge receipt of this email.

Thank you,
Kim

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Friday, July 24, 2015 7:57 AM
To: Tzeng, Linhua
Cc: Carioti, Theresa; Scott, Kimberly
Subject: FW: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Dear Linhua,

I sent the e-mail below to Kimberly Scott and I received an automated reply stating that she will be out of the office until July 27, 2015. The automated e-mail indicated to contact you for matters that cannot wait until her return.

During our teleconference with the Agency on July 15, 2015, we agreed to submit a proposal by 9:00AM (ET) on July 24, 2015.

Please see the attached documents pertaining to our proposal. The documents include:

- Proposed updates to the prescribing information for TREANDA (a “clean” version and a “tracked changes” version in Word)
- Proposed Dear Healthcare Provider (DHCP) letter to communicate compatibility data and changes to the USPI
-  (b) (4)

Please confirm receipt of this e-mail and please feel free to contact me with any questions.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Mike McGraw
Sent: Friday, July 24, 2015 7:39 AM
To: 'Scott, Kimberly'
Cc: Carioti, Theresa; Cox, Toni-Ann
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Dear Kimberly,

During our teleconference on July 15, 2015, we agreed to submit a proposal by 9:00AM on July 24, 2015.

Please see the attached documents pertaining to our proposal. The documents include:

- Proposed updates to the prescribing information for TREANDA (a "clean" version and a "tracked changes" version in Word)
- Proposed Dear Healthcare Provider (DHCP) letter to communicate compatibility data and changes to the USPI
- [REDACTED] (b) (4)

These documents will be formally submitted to NDA 022249 today.

Please confirm receipt of this e-mail and please feel free to contact me with any questions.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Friday, July 17, 2015 9:49 AM
To: Mike McGraw
Cc: Carioti, Theresa; Cox, Toni-Ann
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Good morning Mike,

I am acknowledging receipt of your email, and will be providing you with the list of participants from the Agency soon.

Thank you,

Kim

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Thursday, July 16, 2015 7:52 AM
To: Scott, Kimberly
Cc: Carioti, Theresa; Cox, Toni-Ann
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon

Dear Kimberly,

Thank you very much for meeting with us yesterday to discuss Treanda solution.

Here is the list of attendees from Teva:

Susan Franks, Vice President, Regulatory Affairs
Michael McGraw, Director, Regulatory Affairs
Shirley Speer, Senior Manager, CMC Regulatory Affairs
Donald Hora, Jr., Senior Manager, Labeling Regulatory Affairs
Leonard James, Director, Pharmacovigilance
Pixyish Patel, Senior Director, Pharmaceutical Development
Mehran Yazdanian, Senior Director, Analytical Development and Validation
Barry Brooks, Senior Director, Quality Assurance
David Bonilla, Associate Director, Quality and Compliance
Ashutosh Pathak, Senior Director, Medical Affairs
Susan Larijani, Senior Director, Medical Information
Joan Cappola, Senior Manager, Medical Affairs

We will submit our proposal by 9:00AM on Friday, July 24, 2015 as requested.

Can you please provide a list of FDA attendees?

Regards,
Mike

	Michael J. McGraw Director, Regulatory Affairs Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230 Mike.McGraw@tevapharm.com www.tevapharm.com
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From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, July 09, 2015 1:16 PM
To: Mike McGraw
Cc: Carioti, Theresa; Cox, Toni-Ann; Dennis Ahern; Scott, Kimberly
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Good afternoon Mike,

Thank you for confirming and sending your teleconference number and code for the meeting next Wednesday, July 15, 2015 from 11:30AM-12:00PM (ET). The Agency will be discussing the compatibility data Teva submitted with respect to Treanda solution.

Thanks,

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

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]

Sent: Thursday, July 09, 2015 7:38 AM

To: Scott, Kimberly

Cc: Carioti, Theresa; Cox, Toni-Ann; Dennis Ahern

Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon

Dear Kimberly,

The Teva team is available for a teleconference next Wednesday.

Here are the phone numbers and code for the conference:



We would like to discuss the FDA's comments on the compatibility data we've submitted and the Agency's current thinking with respect to TREANDA solution.

Are there any specific topics that the Agency would like to discuss during this call?

We look forward to speaking with you.

Regards,

Mike



From: Dennis Ahern

Sent: Wednesday, July 08, 2015 3:41 PM

To: Scott, Kimberly;  (b) (6)

Cc: Mike McGraw; Carioti, Theresa; Cox, Toni-Ann

Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon

Hi Kim,

Mike is on vacation today and wanted me to pass along that we need to confirm availability for Teva members and we'll get back to you tomorrow.

Have a nice night!

Dennis



Dennis E. Ahern Sr Dir, Global Regulatory Affairs
Tel: +1-610-786-7379 Cell: +1-215-264-9434
Dennis.Ahern@tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, July 08, 2015 3:31 PM
To: ^{(b) (6)} Dennis Ahern
Cc: Mike McGraw; Carioti, Theresa; Cox, Toni-Ann; Scott, Kimberly
Subject: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Good afternoon Mike,

The Agency is requesting Teva be available to discuss NDA 22249 Treanda by teleconference next Wednesday, July 15, 2015 from 11:30AM – 12:00PM (ET). Please let me know if you and your team are available. If so, please provide a phone number for the conference.

Please acknowledge 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]

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Wednesday, July 01, 2015 11:37 AM
To: Cox, Toni-Ann; Scott, Kimberly
Cc: Shirley Speer
Subject: RE: NDA 022249 S-019- Agency Requests Information DUE July 1

Dear Toni,

Thank you for your response.

I understand that it might be difficult to schedule a teleconference with the upcoming holiday weekend, but I appreciate any attempt you can make to coordinate a call with the review team.

I look forward to hearing from you.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Cox, Toni-Ann [<mailto:Toni-Ann.Cox@fda.hhs.gov>]
Sent: Wednesday, July 01, 2015 11:20 AM
To: Mike McGraw; Scott, Kimberly
Cc: Shirley Speer
Subject: RE: NDA 022249 S-019- Agency Requests Information DUE July 1
Importance: High

Hi Mike,

I confirm receipt of your response on Kim's behalf. I will check with the review team regarding an informal teleconference however given the upcoming holiday, a response may not be available until next week.

Best Regards,
Toni

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Wednesday, July 01, 2015 10:18 AM
To: Scott, Kimberly
Cc: Cox, Toni-Ann; Shirley Speer
Subject: RE: NDA 022249 S-019- Agency Requests Information DUE July 1
Importance: High

Dear Kimberly,

Please see attached our response to the reviewers comments/questions that we received on June 24th.

This response will also be formally submitted to NDA 022249.

Please confirm receipt of this response.

Also, can you confirm whether the reviewers are available for a brief teleconference to discuss this response and the Agency's current thinking with respect to TREANDA solution, as per my e-mail below?

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Mike McGraw
Sent: Monday, June 29, 2015 1:43 PM
To: 'Scott, Kimberly'
Cc: 'Cox, Toni-Ann'; Shirley Speer
Subject: RE: NDA 022249 S-019- Agency Requests Information DUE July 1

Dear Kimberly,

We received comments/questions from the CMC reviewers for TREANDA on June 24th regarding the compatibility data submitted to NDA 022249 on April 1st, 16th, and June 4th (for which we will provide our written responses on July 1st, as requested). We have also received requests from the Division of Hematology Products (DHP) for reports of complaints/inquiries since approval of the labeling supplement (S-019) on March 16th, 25th, May 19th, and most recently on June 24th. The most recent response was submitted to NDA 022249 on June 25th. During a discussion with Dr. Robert Kane, Deputy Director of Safety, on June 3rd, we also agreed to formalize a request for quarterly reports of complaints to be submitted through March 2017. This request is now a postmarketing commitment as per the letter from DHP dated June 5th.

On June 22nd, Teva received the following question from Leo Zadecky, RPh, Senior Program Management Officer, Drug Shortage Staff:

“I am wondering if you can give us a picture of your current inventory for all presentations of the Treanda product (Bendamustine HCL). Are you in backorder status for any of these presentations ? Additionally, could you provide the monthly burn rate for each of the presentations?”

On June 26th, Teva received the following question from CMDR Zadecky:

“How long is Teva capable of covering the market demand with only the powder formulation? When are the next planned campaigns for the powder formulations and when would they be into distribution?”

(b) (4)

Based on the interactions summarized above, we would like to request a brief teleconference with FDA to discuss the recent comments on the compatibility data from your e-mail below and the Agency's current thinking with respect to TREANDA solution.

We understand that the Independence Day holiday is approaching, but please let me know if the Agency is available this week or next week to discuss these issues in an informal teleconference.

We look forward to hearing from you.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

26 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KIMBERLY L SCOTT
08/18/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, July 31, 2015 6:18 AM
To: 'Mike McGraw'
Cc: Shirley Speer; Donald Hora Jr
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11

Dear Mike,

Thank you for confirming Teva teams availability and providing the number for the teleconference Tuesday, August 11, 2015.

Regards,
Kimberly

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

From: Mike McGraw [mailto:Mike.McGraw@tevapharm.com]
Sent: Thursday, July 30, 2015 10:47 PM
To: Scott, Kimberly
Cc: Shirley Speer; Donald Hora Jr
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11

Dear Kimberly,

The Teva team is available for a teleconference on August 11, 2015 from 9:15-10:00AM (ET).

Here is the phone number for the conference:

[REDACTED] (b) (4)
[REDACTED]

Please let me know if you have any questions.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Mike McGraw
Sent: Thursday, July 30, 2015 2:35 PM
To: 'Scott, Kimberly'
Cc: Shirley Speer; Donald Hora Jr
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11
Importance: High

Dear Kimberly,

I confirm receipt of your e-mail.

I will contact the Teva team and confirm availability as soon as possible.

Are there any specific issues within the proposals that the Agency would like to discuss?

Please note that I will be out of the office next week and beginning tomorrow. If you have any questions or issues during that time, please send them to my colleagues, Shirley Speer and Donald Hora (both copied here), and copy me.

Please let me know if you have any questions.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, July 30, 2015 2:05 PM
To: Mike McGraw
Subject: NDA 022249 Treanda: Agency requesting Teleconference, Tuesday, 8/11
Importance: High

Good afternoon Mike,

The Agency is requesting Teva be available to discuss NDA 22249 Treanda via teleconference Tuesday, August 11, 2015 from 9:15AM – 10:00AM (ET). The Agency will be discussing the proposals Teva sent via email on Friday, July 24, 2015.

Please let me know if you and your team are available. If so, please provide a phone number for the conference.

Please acknowledge receipt of this email.

Thank you,
Kim

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Friday, July 24, 2015 7:57 AM
To: Tzeng, Linhua

Cc: Carioti, Theresa; Scott, Kimberly

Subject: FW: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon

Importance: High

Dear Linhua,

I sent the e-mail below to Kimberly Scott and I received an automated reply stating that she will be out of the office until July 27, 2015. The automated e-mail indicated to contact you for matters that cannot wait until her return.

During our teleconference with the Agency on July 15, 2015, we agreed to submit a proposal by 9:00AM (ET) on July 24, 2015.

Please see the attached documents pertaining to our proposal. The documents include:

- Proposed updates to the prescribing information for TREANDA (a "clean" version and a "tracked changes" version in Word)
- Proposed Dear Healthcare Provider (DHCP) letter to communicate compatibility data and changes to the USPI
- [REDACTED] (b) (4)

Please confirm receipt of this e-mail and please feel free to contact me with any questions.

Regards,
Mike

 **Michael J. McGraw** Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Mike McGraw
Sent: Friday, July 24, 2015 7:39 AM
To: 'Scott, Kimberly'
Cc: Carioti, Theresa; Cox, Toni-Ann
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Dear Kimberly,

During our teleconference on July 15, 2015, we agreed to submit a proposal by 9:00AM on July 24, 2015.

Please see the attached documents pertaining to our proposal. The documents include:

- Proposed updates to the prescribing information for TREANDA (a "clean" version and a "tracked changes" version in Word)
- Proposed Dear Healthcare Provider (DHCP) letter to communicate compatibility data and changes to the USPI
- [REDACTED] (b) (4)

These documents will be formally submitted to NDA 022249 today.

Please confirm receipt of this e-mail and please feel free to contact me with any questions.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Friday, July 17, 2015 9:49 AM
To: Mike McGraw
Cc: Carioti, Theresa; Cox, Toni-Ann
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Good morning Mike,

I am acknowledging receipt of your email, and will be providing you with the list of participants from the Agency soon.

Thank you,
Kim

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Thursday, July 16, 2015 7:52 AM
To: Scott, Kimberly
Cc: Carioti, Theresa; Cox, Toni-Ann
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon

Dear Kimberly,

Thank you very much for meeting with us yesterday to discuss Treanda solution.

Here is the list of attendees from Teva:

Susan Franks, Vice President, Regulatory Affairs
Michael McGraw, Director, Regulatory Affairs
Shirley Speer, Senior Manager, CMC Regulatory Affairs
Donald Hora, Jr., Senior Manager, Labeling Regulatory Affairs
Leonard James, Director, Pharmacovigilance
Pixyish Patel, Senior Director, Pharmaceutical Development
Mehran Yazdanian, Senior Director, Analytical Development and Validation
Barry Brooks, Senior Director, Quality Assurance
David Bonilla, Associate Director, Quality and Compliance
Ashutosh Pathak, Senior Director, Medical Affairs
Susan Larijani, Senior Director, Medical Information
Joan Cappola, Senior Manager, Medical Affairs

We will submit our proposal by 9:00AM on Friday, July 24, 2015 as requested.

Can you please provide a list of FDA attendees?

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, July 09, 2015 1:16 PM
To: Mike McGraw
Cc: Carioti, Theresa; Cox, Toni-Ann; Dennis Ahern; Scott, Kimberly
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Good afternoon Mike,

Thank you for confirming and sending your teleconference number and code for the meeting next Wednesday, July 15, 2015 from 11:30AM-12:00PM (ET). The Agency will be discussing the compatibility data Teva submitted with respect to Treanda solution.

Thanks,

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]

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Thursday, July 09, 2015 7:38 AM
To: Scott, Kimberly
Cc: Carioti, Theresa; Cox, Toni-Ann; Dennis Ahern
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon

Dear Kimberly,

The Teva team is available for a teleconference next Wednesday.

Here are the phone numbers and code for the conference:

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]

We would like to discuss the FDA's comments on the compatibility data we've submitted and the Agency's current thinking with respect to TREANDA solution.

Are there any specific topics that the Agency would like to discuss during this call?

We look forward to speaking with you.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Dennis Ahern
Sent: Wednesday, July 08, 2015 3:41 PM
To: Scott, Kimberly; (b) (6)
Cc: Mike McGraw; Carioti, Theresa; Cox, Toni-Ann
Subject: RE: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon

Hi Kim,
Mike is on vacation today and wanted me to pass along that we need to confirm availability for Teva members and we'll get back to you tomorrow.
Have a nice night!
Dennis



Dennis E. Ahern Sr Dir, Global Regulatory Affairs
Tel: +1-610-786-7379 Cell: +1-215-264-9434
Dennis.Ahern@tevapharm.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, July 08, 2015 3:31 PM
To: (b) (6) Dennis Ahern
Cc: Mike McGraw; Carioti, Theresa; Cox, Toni-Ann; Scott, Kimberly
Subject: NDA 022249 Treanda: Agency requesting Teleconference, 7/15 @ 11:30-12noon
Importance: High

Good afternoon Mike,

The Agency is requesting Teva be available to discuss NDA 22249 Treanda by teleconference next Wednesday, July 15, 2015 from 11:30AM - 12:00PM (ET). Please let me know if you and your team are available. If so, please provide a phone number for the conference.

Please acknowledge 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

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Wednesday, July 01, 2015 11:37 AM
To: Cox, Toni-Ann; Scott, Kimberly
Cc: Shirley Speer
Subject: RE: NDA 022249 S-019- Agency Requests Information DUE July 1

Dear Toni,

Thank you for your response.

I understand that it might be difficult to schedule a teleconference with the upcoming holiday weekend, but I appreciate any attempt you can make to coordinate a call with the review team.

I look forward to hearing from you.

Regards,
Mike

	Michael J. McGraw Director, Regulatory Affairs Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230 Mike.McGraw@tevapharm.com www.tevapharm.com
-----------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------

From: Cox, Toni-Ann [<mailto:Toni-Ann.Cox@fda.hhs.gov>]
Sent: Wednesday, July 01, 2015 11:20 AM
To: Mike McGraw; Scott, Kimberly
Cc: Shirley Speer
Subject: RE: NDA 022249 S-019- Agency Requests Information DUE July 1
Importance: High

Hi Mike,

I confirm receipt of your response on Kim's behalf. I will check with the review team regarding an informal teleconference however given the upcoming holiday, a response may not be available until next week.

Best Regards,
Toni

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Wednesday, July 01, 2015 10:18 AM
To: Scott, Kimberly
Cc: Cox, Toni-Ann; Shirley Speer
Subject: RE: NDA 022249 S-019- Agency Requests Information DUE July 1
Importance: High

Dear Kimberly,

Please see attached our response to the reviewers comments/questions that we received on June 24th.

This response will also be formally submitted to NDA 022249.

Please confirm receipt of this response.

Also, can you confirm whether the reviewers are available for a brief teleconference to discuss this response and the Agency's current thinking with respect to TREANDA solution, as per my e-mail below?

Regards,
Mike

	Michael J. McGraw Director, Regulatory Affairs Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230 Mike.McGraw@tevapharm.com www.tevapharm.com
-----------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------

From: Mike McGraw
Sent: Monday, June 29, 2015 1:43 PM
To: 'Scott, Kimberly'
Cc: 'Cox, Toni-Ann'; Shirley Speer
Subject: RE: NDA 022249 S-019- Agency Requests Information DUE July 1

Dear Kimberly,

We received comments/questions from the CMC reviewers for TREANDA on June 24th regarding the compatibility data submitted to NDA 022249 on April 1st, 16th, and June 4th (for which we will provide our written responses on July 1st, as requested). We have also received requests from the Division of Hematology Products (DHP) for reports of complaints/inquiries since approval of the labeling supplement (S-019) on March 16th, 25th, May 19th, and most recently on June 24th. The most recent response was submitted to NDA 022249 on June 25th. During a discussion with Dr. Robert Kane, Deputy Director of Safety, on June 3rd, we also agreed to formalize a request for quarterly reports of complaints to be submitted through March 2017. This request is now a postmarketing commitment as per the letter from DHP dated June 5th.

On June 22nd, Teva received the following question from Leo Zadecky, RPh, Senior Program Management Officer, Drug Shortage Staff:

“I am wondering if you can give us a picture of your current inventory for all presentations of the Treanda product (Bendamustine HCL). Are you in backorder status for any of these presentations ? Additionally, could you provide the monthly burn rate for each of the presentations?”

On June 26th, Teva received the following question from CMDR Zadecky:

“How long is Teva capable of covering the market demand with only the powder formulation? When are the next planned campaigns for the powder formulations and when would they be into distribution?”

(b) (4)

Based on the interactions summarized above, we would like to request a brief teleconference with FDA to discuss the recent comments on the compatibility data from your e-mail below and the Agency's current thinking with respect to TREANDA solution.

We understand that the Independence Day holiday is approaching, but please let me know if the Agency is available this week or next week to discuss these issues in an informal teleconference.

We look forward to hearing from you.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

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

/s/

KIMBERLY L SCOTT

07/31/2015

Agency requesting TCON on August 11, 2015 to discuss proposed plan Teva sent on July 24, 2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, July 07, 2015 11:55 AM
To: Mike McGraw (Mike.McGraw@tevapharm.com)
Cc: Cox, Toni-Ann; Carioti, Theresa; Scott, Kimberly
Subject: NDA 022249 S-019- Agency Requests Information DUE July 9

Importance: High

Good afternoon Mike,

The Agency received your April 16, 2015 submission for NDA 22249, Teva's compatibility of IV infusion sets with Treanda liquid. The Agency requests Teva respond by **Noon, Thursday, July 9, 2015** to the following questions:

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).
 - 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.

Please respond to the questions by **Noon, Thursday, July 9, 2015**, by email as well as officially submitting in triplicate, to the IND. I will be out of the office July 9, 2015 through July 13, 2015. Please be sure to copy me and Toni-Ann Cox (cc'd on this email) on any correspondences.

[Please acknowledge receipt of this email.](#)

Thank you,
Kimberly
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

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

/s/

KIMBERLY L SCOTT
07/07/2015



NDA 22249/S-019

NEW POSTMARKETING COMMITMENT

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 refer to your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Treanda[®] (bendamustine hydrochloride) Injection (solution) 45 mg/0.5 mL or 180mg/2mL and Treanda[®] (bendamustine hydrochloride) for Injection (lyophilized powder), 25 mg/vial or 100mg/vial.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We have received your letter dated April 28, 2015, stating your commitment to conduct the following postmarketing study:

PMC 2915-1: Submit and analyze quarterly reports until March 2017 of complaints about preparation and use of Treanda Injection (solution) and Treanda for Injection (lyophilized powder).

The timetable you submitted on April 28, 2015, states that you will conduct this study according to the following timetable:

Interim Report (March 1, 2015, through May 31, 2015):	June 2015
Interim Report (June 1, 2015, through August 31, 2015):	September 2015
Interim Report (September 1, 2015, through November 30, 2015):	December 2015
Interim Report (December 1, 2015, through February 29, 2016):	March 2016
Interim Report (March 1, 2016, through May 31, 2016):	June 2016
Interim Report (June 1, 2016, through August 31, 2016):	September 2016
Interim Report (September 1, 2016, through November 30, 2016):	December 2016
Interim Report (December 1, 2016, through February 28, 2017):	March 2017
Study Completion:	March 2017
Final Report Submission:	June 2017

Submit all interim and final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii), include a status summary of each commitment in your annual report to this NDA. The status

summary should include expected study/trial completion and final report submission dates, any changes in plans since the last annual report, and, for studies/trials, the number of patients entered into each study/trial. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled **“Postmarketing Protocol,” “Postmarketing Final Report,” or “Postmarketing Correspondence.”**

If you have any questions, call Ms. Diane Leaman, Safety Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Robert C. Kane, MD.
Deputy Director for Safety
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

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

/s/

ROBERT C KANE
06/05/2015



NDA 22249

MEETING MINUTES

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

Dear Dr. McGraw:

Please refer to your New Drug Application (NDA) dated submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Treanda[®] (bendamustine hydrochloride) Injection and Treanda[®] (bendamustine hydrochloride) for Injection.

We also refer to the telecon between representatives of your firm and the FDA on June 3, 2015. The purpose of the meeting was to respond to your May 29, 2015, email regarding the submission of quarterly reports of complaints regarding preparation and use of Treanda (bendamustine hydrochloride).

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Safety Regulatory Project Manager
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: General Advice

Meeting Date and Time: June 3, 2015; 3:10 PM
Meeting Location: White Oak

Application Number: NDA 22249
Product Name: Treanda[®] (bendamustine hydrochloride) Injection and Treanda[®] (bendamustine hydrochloride) for Injection
Indication: 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.
TREANDA is also 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.

Sponsor/Applicant Name: Cephalon

Meeting Chair: Robert C. Kane, MD
Meeting Recorder: Diane Leaman, SRPM

FDA ATTENDEES

Robert C. Kane, MD, Deputy Director for Safety, DHP
Diane Leaman, SRPM, DHP

SPONSOR ATTENDEES

Michael J. McGraw, PharmD, MS, Director, Regulatory Affairs, Cephalon

1.0 BACKGROUND

On May 29, 2015, Cephalon inquired via email to Kimberly Scott, RPM (see appended), the status of their proposal for the dates for submitting agreed up complaint submissions regarding the preparation and use of Treanda. This meeting is to provide a brief comment to address the question and to advise Teva of our intent to formalize the request for quarterly reporting in the form of a post-marketing commitment (PMC).

2. DISCUSSION

Item 1: Treanda and Submission of Quarterly Reports of Complaints

FDA Comments:

The March 10, 2015 approval letter asked for quarterly reports to March 2017 with the use of Treanda. The Applicant's response was fine. The Agency wants to formalize the items in the approval letter with a Post Marketing Commitment to put it into standard format and listing the quarterly reports and the due dates. We have reviewed the Applicant's proposed dates in their April 28, 2015, submission.

The Applicant replied that the plan to issue a PMC to describe the agreed upon reporting process is acceptable. The first quarterly report would cover the dates proposed from March through the end of May to be reported by the end of June.

The Agency noted that they would be sending Cephalon a letter with the list of dates, which will be the same dates as proposed by Cephalon. The letter will also document when the final agreed upon submission would be for these reports. The Agency also noted that if Cephalon feels that the submission of these reports should be stopped prior to the 2017 date as planned in the letter, they could submit their rationale at an earlier time for our consideration.

The Applicant asked if the Agency had received any complaints regarding the use of Treanda with closed system devices. The Agency responded that we have not received anything specific in that regard.

Item 2: Testing of the closed system transfer devices

FDA Comments:

The Agency noted that they had received the report from Cephalon on the testing of the close system transfer devices and it will take some time for the chemistry reviewers to review it. Cephalon noted that there will be more results sent on June 4, 2015, on testing the closed system transfer devices. The Agency noted that it might be good to look at the composition of the devices being tested, as well as the names of the manufacturers as there may be multiple different formulations for a manufacturer's devices, such as is the case for gloves. A single manufacturer may have a number of devices, such as gloves, of varying compositions, in which case designating a product by reference only to the manufacturer name may not adequately describe the multiple product compositions for a given device.

Cephalon thanked the Agency for the recommendation.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Send PMC letter	FDA	Within the next two weeks
Submit further testing with	Applicant	June 4, 2015 and

closed system transfer devices		subsequently, as needed
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6.0 ATTACHMENTS AND HANDOUTS

Email string

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Friday, May 29, 2015 11:38 AM
To: Scott, Kimberly
Subject: RE: TREANDA - NDA 022249 -Quarterly Reports of complaints
Importance: High

Dear Kimberly,

On April 28, 2015 we submitted our proposal for the submission of quarterly reports of complaints as requested in the supplement approval letter dated March 10, 2015 for supplement S-019.

We requested the Agency's feedback on the proposed reporting periods, due dates, and the content of the reports. We recently responded to FDA's request for information on May 20, 2015 (see below) regarding reports received after the PI was revised on March 10, 2015.

According to our proposal, the first report would be due by June 30, 2015 and the first reporting period would be March 1, 2015 through May 31, 2015.

Can you please provide an update on the status of the review of our proposal?

Many thanks for your help and have a nice weekend.

Regards,
Mike

 **Michael J. McGraw** Director, Regulatory Affairs
Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

From: Mike McGraw
Sent: Wednesday, May 20, 2015 12:39 PM
To: 'Scott, Kimberly'
Subject: RE: TREANDA - NDA 022249 -Quarterly Reports of complaints

Dear Kimberly,

Please see below the summary of complaints received since the USPI was revised on March 10, 2015:

- 63 total contacts were received between 3/10/2015 through 5/19/2015, these contacts were received by Quality Assurance Services as Complaints. There were no new safety issues to those previously identified during this review period.
 - 55 contacts were for product compatibility related inquiries or use of the Treanda with closed system transfer devices (CSTDs).
 - 1 of them resulted in adverse event and concerns use of a CSTD with Treanda and skin issues. The case details were very limited precluding an adequate assessment of the case. Follow up has been requested.
 - 1 contact was for difficult to dispense the total quantity in the vials.
 - 3 contacts were related to lack of effect of an injectable bendamustine, reports were received via MedWatch without lot # and could not be confirmed if it was Treanda.
 - 2 contacts were related to mishandling by the customer (incorrect storage and vials dropped on the floor).
 - 2 contacts were related to visible particulate or discoloration used in conjunction with close deliver systems non Teva device.

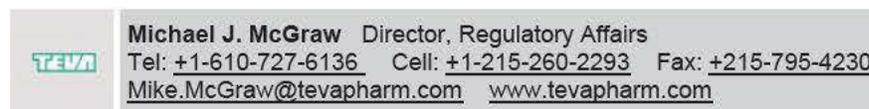
Please note that the contacts above represent a total of 64 reasons/lots. This is due to some contacts resulting in requests for multiple types of information or lots.

- There is one occupational exposure that was initially reported as a complaint prior to 3/10/2015 but further details were obtained during this reporting period (3/10/2015 through 5/19/2015) and it is being added to this report. The case concerns a pharmacist who was using a CSTD (non-Teva device) and during withdrawal using a second CSTD, the device melted into two pieces causing leakage of the solution. The pharmacist experienced brief upper respiratory irritation/inflammation, cough, fatigue, confusion and dizziness. The cough did not resolve, however the remaining events were self-limiting and resolved.

This response will also be submitted formally to the NDA.

Please contact me with any further questions. We look forward to receiving FDA's comments on our proposal for the content and timelines of quarterly report submissions.

Regards,
Mike



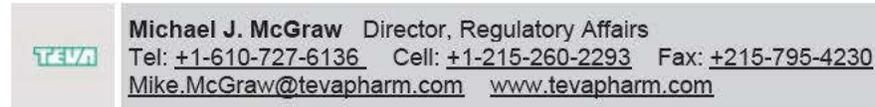
From: Mike McGraw
Sent: Tuesday, May 19, 2015 3:28 PM
To: 'Scott, Kimberly'
Subject: RE: TREANDA - NDA 022249 -Quarterly Reports of complaints

Dear Kimberly,

Thank you very much for the clarification.

I will contact the team and confirm that we can respond by noon tomorrow.

Regards,
Mike



From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, May 19, 2015 3:26 PM
To: Mike McGraw
Cc: Scott, Kimberly
Subject: RE: TREANDA - NDA 022249 -Quarterly Reports of complaints
Importance: High

Dear Mike,

The Agency is requesting reports for those received after the date of the revised PI.

Cases are defined as “new” if they describe something not previously described. Melting of the hub, for example, is not a “new” issue. Therefore, we need for Teva to differentiate between follow-up on the already known issues versus any “new” safety issues that we were not previously aware of.

Thank you,
Kimberly
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

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Tuesday, May 19, 2015 2:59 PM
To: Scott, Kimberly
Subject: RE: TREANDA - NDA 022249 -Quarterly Reports of complaints
Importance: High

Dear Kimberly,

I confirm receipt of your e-mail.

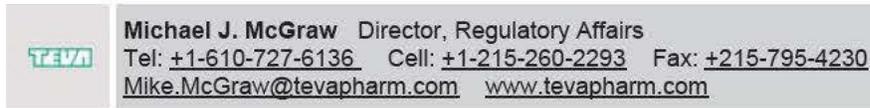
Can you please confirm the time period for the reports?

Does FDA want all reports of complaints received to date regarding the Treanda liquid formulation? Or Does FDA want all reports of complaints received for Treanda since the product was first approved in March 2008?

When you say to “sort the reports by ‘pre-existing’ safety issues (similar to the ones previously reported), versus ‘new’ issues identified”, do you mean to separate by cases we provided in prior requests for information versus cases received since FDA’s last request for complaints?

Please confirm the details of this request or please feel free to call me to discuss.

Regards,
Mike



From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, May 19, 2015 2:49 PM
To: Mike McGraw
Cc: Scott, Kimberly
Subject: RE: TREANDA - NDA 022249 -Quarterly Reports of complaints
Importance: High

Dear Mike,

The Agency is requesting Teva submit all reports of complaints for Treanda, NDA 22249 by tomorrow, May 20, 2015 at 12:00pm (ET). Please sort the reports by “pre-existing” safety issues (similar to the ones previously reported), versus “new” issues identified.

Please acknowledge receipt of this email.

Thank you,
Kimberly
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

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Tuesday, April 28, 2015 2:05 PM
To: Scott, Kimberly
Cc: Carioti, Theresa
Subject: TREANDA - NDA 022249 - Proposal for submission of quarterly reports of complaints

Dear Kimberly,

Today we submitted our proposal for the submission of quarterly reports of complaints as requested in the supplement approval letter dated March 10, 2015 for supplement S-019.

We are requesting the Agency's feedback on the proposed reporting periods, due dates, and the content of the reports. Please see the attached cover letter for your reference.

According to our proposal, the first report would be due by June 30, 2015 so we would appreciate a response by May 26, 2015 so that we have time to address FDA's comments, if any, prepare the first quarterly report, and submit the report as requested.

Please confirm receipt and we look forward to receiving a response from the Agency.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
Tel: [+1-610-727-6136](tel:+1-610-727-6136) Cell: [+1-215-260-2293](tel:+1-215-260-2293) Fax: [+215-795-4230](tel:+215-795-4230)
Mike.McGraw@tevapharm.com www.tevapharm.com

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/s/

DIANE V LEAMAN
06/04/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, May 19, 2015 3:26 PM
To: Mike McGraw
Cc: Scott, Kimberly
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Thank you,

Kimberly

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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Sent: Tuesday, May 19, 2015 2:59 PM
To: Scott, Kimberly
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Importance: High

Dear Kimberly,

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Regards,
Mike



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Tel: +1-610-727-6136 Cell: +1-215-260-2293 Fax: +215-795-4230
Mike.McGraw@tevapharm.com www.tevapharm.com

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To: Mike McGraw
Cc: Scott, Kimberly
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Importance: High

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Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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To: Scott, Kimberly
Cc: Carioti, Theresa
Subject: TREANDA - NDA 022249 - Proposal for submission of quarterly reports of complaints

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Please confirm receipt and we look forward to receiving a response from the Agency.

Regards,
Mike



Michael J. McGraw Director, Regulatory Affairs
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Mike.McGraw@tevapharm.com www.tevapharm.com

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/s/

KIMBERLY L SCOTT
05/20/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, March 25, 2015 12:04 PM
To: Mike McGraw (Mike.McGraw@tevapharm.com)
Cc: Carioti, Theresa; Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)
Subject: sNDA 22249/S019 Treanda- REVIEW email before sending to Teva

Importance: High

Dear Mike,

The Agency is aware that there appears to be conflicting information from the device manufacturers and Teva regarding compatibility with Treanda injection and closed system transfer devices.

The Agency would like to discuss with Teva the plans moving forward. Please be prepared to discuss the following:

- [REDACTED] (b) (4)
- Has Teva received any additional inquiries or complaints since our last meeting, March 16, 2015?

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.

Please acknowledge receipt of this correspondence.

Thank you,

Kimberly

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

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]

Sent: Wednesday, March 25, 2015 8:39 AM

To: Scott, Kimberly

Subject: RE: sNDA 22249/S019 Treanda

Dear Kimberly,

Thank you very much for your response.

If you receive comments or questions from the reviewers, can you provide any comments before the meeting so that we can address them during our teleconference?

Regards,
Mike

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, March 25, 2015 7:51 AM
To: Mike McGraw
Subject: RE: sNDA 22249/S019 Treanda
Importance: High

Good morning Mike,

I am scheduling a teleconference in the event the reviewers decide they would like to discuss the results of your compatibility study. I would suggest having your entire team available. I should know more this morning.

Thank you,
Kimberly

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

From: Mike McGraw [<mailto:Mike.McGraw@tevapharm.com>]
Sent: Tuesday, March 24, 2015 3:50 PM
To: Scott, Kimberly
Subject: RE: sNDA 22249/S019 Treanda
Importance: High

Dear Kim,

I am confirming the availability of the Teva team members for tomorrow's teleconference.

Can you elaborate further on the reviewers' comments or questions regarding the compatibility data so that I can ensure that we have the correct team members on the line to respond to any questions?

Thank you very much.

Regards,
Mike

From: Mike McGraw
Sent: Tuesday, March 24, 2015 3:24 PM
To: 'Scott, Kimberly'
Subject: RE: sNDA 22249/S019 Treanda

Dear Kim,

I confirm receipt of your e-mail.

The teleconference number is below:

 (b) (4)

Please let me know if you have any questions.

Regards,
Mike

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, March 24, 2015 3:05 PM
To: Mike McGraw
Subject: sNDA 22249/S019 Treanda
Importance: High

Good afternoon Mike,

The Agency is reviewing the compatibility data you submitted to the NDA yesterday, March 23, 2015. I would like to set up a teleconference for our team to discuss the results with Teva for tomorrow afternoon from 2:30pm-3:00pm. Please be sure to send me a teleconference number that we can contact you, and your team.

Please acknowledge receipt of this email.

Thank you,
Kimberly

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
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Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
03/25/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, March 10, 2015 10:18 AM
To: Mike McGraw (Mike.McGraw@tevapharm.com)
Cc: Carioti, Theresa; Nina Moore (Nina.Moore@tevapharm.com); Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)
Subject: NDA 22249 Treanda FDA Edits to USPI Label Please review and respond by 11:30AM
Attachments: sNDA FDA Edits Lyo and LIiquid label for Treanda March 10 2015.doc
Importance: High

Good morning Mike,

As per our discussion yesterday, the Agency is providing Teva with additional edits to the Treanda prescribing information. We need your response by no later than 11:30am today. Please indicate your acceptance of the proposed changes, by accepting FDA's edits. If you make further edits, please do so in "track changes," and send your response by email followed by a formal submission to NDA 22249/S-019.

Please note that the Supplement submitted on March 6, 2015 is listed as S-019. Could you also submit your DHCP letter to your Supplement?

Thank you,
Kimberly

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
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/s/

KIMBERLY L SCOTT
03/10/2015