DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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 Unites 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 Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

## CARTON AND IMMEDIATE CONTAINER LABELS

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 [redacted] (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. Trean*XXXX*) 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.

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

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