CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 19, 2008
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	22-249
Applicant Name	Cephalon, Inc.
Date of Submission	September 20, 2007
PDUFA Goal Date	March 20, 2008
Proprietary Name / Established (USAN) Name	TREANDA/bendamustine HCl
Dosage Forms / Strength	Single-use vial containing 100 mg of bendamustine HCl as lyophilized powder
Proposed Indication(s)	TREANDA (bendamustine hydrochloride) for Injection is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Reviews	3/5/08
Statistical Reviews	2/19/08
Pharmacology Toxicology Reviews	2/27/08, 3/11/08
CMC Review/OBP Review	2/27/08, 3/19/08
Microbiology Reviews	12/17/07, 2/6/08
Clinical Pharmacology Reviews	2/19/08, 2/22/08
DDMAC	3/3/08
DSI	2/28/08
CDTL Review	3/5/08
OSE/DMEP	3/6/08
OSE/DDRE	N/A
OSE/DSRCS	N/A
SEALD	2/19/08

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEP=Division of Medication Error Prevention
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This new drug application seeks approval of TREANDA for the following indication:

> TREANDA (bendamustine hydrochloride) for Injection is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.

The application was submitted on September 20, 2007 and the PDUFA goal date is March 20, 2008. This review will summarize the efficacy and safety data supporting approval, the recommendations of each review discipline, and any outstanding issues.

2. Background

Bendamustine is a bifunctional mechlorethamine derivative. Mechlorethamine and its derivatives dissociate into electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties. The bifunctional covalent linkage can lead to cell death via several pathways. The exact mechanism of action of bendamustine remains unknown.

Bendamustine has been marketed in the German Democratic Republic since 1974, in Germany since 1993, and Bulgaria since 2000. It is authorized for the treatment of **Hodgkin's disease, non-Hodgkin's lymphoma,** chronic lymphocytic leukemia, multiple myeloma, and breast cancer.

An IND was submitted in 2003, an end-of-phase 2 meeting was held on 9/2/04, and pre-NDA meetings were held on 4/12/07 and 4/27/07 (CMC). The issue of the potential acceptability of a single randomized trial to support approval was discussed at the EOP2 meeting.

3. CMC/Device

Chemistry Review

The Chemistry Review of 2/27/08 made the following recommendation regarding approval:

> The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act, provided trademark and labeling acceptability has been determined by Office of Drug Safety (DMETS) and provided the manufacturing sites are deemed acceptable for cGMP compliance. The product quality microbiology has recommended approval on 06-Feb-2008. The recommendation for Office of Compliance regarding the acceptability of the manufacturing facilities is pending as of the date of this review.

The review listed the following deficiencies:

1. The following agreement should be placed in the action letter.

We remind you of your agreement in an amendment dated 12-Feb-2008 to initiate change controls for all the documents impacted by the revision to the maximum hold time not to exceed [redacted] and to submit appropriate post-approval correspondence reflecting this change.

2. The company should commit to the following phase 4 commitment:

Provide an agreement to study the physico-chemical compatibility of the drug product with commonly used diluents such as [redacted] and submit the data within six months from the date of approval of this NDA.

CMC Branch Chief Memo

The CMC Branch Chief Memo of 3/19/08 made the following overall recommendation:

All pending issues subsequent to completion of the primary CMC review have been resolved satisfactorily. The Office of Compliance made an acceptable cGMP recommendation for the NDA on March 17, 2008. The DDMAC and DMETs reviews on labels and labeling were completed and the combined CMC/DMETs comments on labels and labeling were satisfactorily addressed by the firm. An approval recommendation is made for this NDA. A statement on grantable expiration dating period and reminders on a CMC post-marketing commitment and a CMC agreement, listed at the end of this memo, have been included in the action letter.

Comment: I concur with the conclusions reached by the chemistry reviewer and branch chief regarding the acceptability of the manufacturing of the drug product and drug substance and the recommended phase 4 commitment. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology Review and Evaluation

The Pharmacology/Toxicology Review and Evaluation dated February 27, 2008 made the following recommendations:

A. Recommendation on approvability: The non-clinical studies submitted to this NDA provide sufficient information to support the use of Treanda ® (bendamustine hydrochloride) for the treatment of patients with chronic lymphocytic leukemia (CLL).
B. Recommendation for nonclinical studies: No additional non-clinical studies are required.
C. Recommendations on labeling: A separate review will be conducted.

The pharmacology/toxicology labeling review was completed on March 11, 2008.

Secondary and Tertiary Pharmacology/Toxicology Reviews
The secondary and tertiary reviews concurred that the pharmacology and toxicology data support approval and that there are no outstanding nonclinical issues.

Comment: I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Review
The Clinical Pharmacology Review of February 19, 2008 made the following recommendations:

> The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in the NDA 22-249.
>
> This NDA is considered to be deficient from a clinical pharmacology perspective due to the lack of data available regarding pharmacokinetics at the proposed dose, dose proportionality, human excretion and metabolism, effect on QT prolongation, in-vivo drug-drug interactions, and in-vitro p-glycoprotein screens.
>
> The NDA will be considered acceptable pending the sponsor's agreement to the following Phase 4 commitments:
>
> Phase IV commitments
>
> 1. Submit the completed report and data sets for the mass-balance evaluation. Results from this study may indicate a need for dedicated renal and/or hepatic organ impairment studies.
>
> 2. The potential for bendamustine to affect the QT interval needs to be investigated.
>
> 3. The influence of CYP1A2 inhibitors (fluvoxamine) on bendamustine pharmacokinetics needs to be evaluated in-vivo.
>
> 4. The influence of CYP1A2 inducers (smoking) on bendamustine pharmacokinetics needs to be evaluating in-vivo.
>
> 5. In-vitro p-glycoprotein screens need to be completed to determine if bendamustine is an inhibitor or substrate of p-glycoprotein.
>
> 6. [redacted]

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