CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo

NDA 22-249
TREANDA®
Date: March 19, 2008

Introduction

TREANDA® (bendamustine HCl) for Injection is a synthetic new molecular entity alkylating agent. It is supplied as a lyophilized powder containing the drug substance (100 mg) and mannitol (170 mg) in 20 mL amber glass vials. At the time of use, the powder is reconstituted with 20 mL Sterile Water for Injection USP to yield a solution of 5 mg/mL bendamustine HCl. This solution is further diluted with normal saline to a concentration of 0.2 to 0.6 mg/mL and administered by IV infusion over 30 minutes.

ONDQA recommends approval.

Administrative

The corresponding IND for this application is 67,554. The NDA was received 19-SEP-2007 was assigned a priority review status (1P) and was part of the GRMP pilot program for Oncology Drug Products. The CMC review was complete as of Feb 27, 2008. At that time, the Environmental Assessment (categorical exclusion justified) and Microbiology reviews (approval recommended) were complete.

However, as per GRMP's the CMC review was completed on the aforementioned date with items NOT under ONDQA control left pending (e.g., EES recommendation). The final recommendation from OC regarding the acceptability of facilities was received 17-MAR-2008 (acceptable overall).

Drug Substance and Drug Product

Bendamustine hydrochloride is a new molecular entity synthetic alkylating agent (nitrogen mustard type). Being a weak base, the solubility in aqueous solvents is pH dependent; being more soluble in acidic media. The drug substance is photosensitive; thus the drug substance is packaged and labeled to be protected from light (

The drug product is a single strength as 100 mg bendamustine HCl plus 170 mg Mannitol, in 20 mL amber glass vials sealed with a rubber stopper topped with a crimped *flip-off* seal. The powder-filled vials are packaged in cardboard containers with the notation to "protect from light" on the side panel of the carton and the notation to "retain in carton until time of use" on the front panel of the carton.

At the time of use, the drug product is reconstituted with with 20 mL Sterile Water for Injection USP to yield a solution of 5 mg/mL bendamustine HCl This solution which is not to be administered may be clear to pale yellow in color.

This is further diluted with normal saline to a concentration of 0.2 to 0.6 mg/mL and administered by IV infusion over 30 minutes. The shelf life of the solution to be infused is three (3) hours at room temperature (including infusion time) or twenty four (24) hours when at 5C.

The lyophilized drug product is stable for 24 months when stored between two (2) and 25 degrees C.

Phase-4 Commitment

The applicant agrees to provide assay and impurity profile data within six (6) months of approval to assess the compatibility and stability of the infusion solution when constituted with other common diluents such as [redacted]

Rik Lostritto, Ph.D., Director
ONDQA, Division-III

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/s/

Richard Lostritto
3/19/2008 04:47:27 PM
CHEMIST

CMC Branch Chief Memo

Application: NDA 22-249. Treanda (Bendamustine Hydrochloride) for Injection
Submission type: 505 (b) (1), Type I (NME)
Applicant: Cephalon, Inc., 41 Moores Road, Frazer, PA 19355
Initial Quality Assessment: Sarah Pope, Ph.D. (IQA in DFS dated 10/10/2007)
Primary CMC reviewer: Ravindra Kasliwal, Ph.D. (Review in DFS dated 2/27/2008)

Overall recommendation:

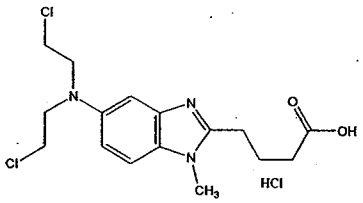
All pending issues subsequent to completion of the primary CMC review have been resolved satisfactorily. The Office of Compliance made an acceptable cGMP recommendation for the NDA on March 17, 2008. The DDMAC and DMETs reviews on labels and labeling were completed and the combined CMC/DMETs comments 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.

Background:

The NDA was reviewed under priority clock (6 months) and was the first GRMP pilot in the Division of Drug Oncology Products. The PDUFA date is March 20, 2008.

Introduction:

Bendamustine HCl is a non-sterile, synthetic alkylating agent containing nitrogen mustard structural element and has known genotoxic nature. Chemically, it is 1H-Benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl) amino]-1-methyl-, monohydrochloride. The USAN and INN name for the drug substance is bendamustine hydrochloride.The primary CMC review indicated that the long-term drug substance stability data support the proposed — retest period when stored at 2°-25°C (36°-77°F) and protected from light (bendamustine HCl is photosensitive).



$C_{16}H_{22}Cl_3N_3O_2$
Mol. Wt.: 394.7
C, 48.69; H, 5.62; Cl, 26.94; N, 10.65; O, 8.11

The TREANDA® (bendamustine HCl) for Injection is packaged as a lyophilized powder in 20-cc amber glass vials in 100 mg strength. Each 100 mg vial is to be reconstituted

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