

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 14, 2008

From: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Branch V, DPAMS, ONDQA

Through: Sarah Pope, Ph.D.
Acting Branch Chief
Branch V, DPAMS, ONDQA

Sponsor: Cephalon, Inc.
41 Moores Rd.
Frazer, PA 19355

Drug: TREANDA[®] (bendamustine hydrochloride) for injection

Subject: CMC review and recommendation for and NDA 22-303 (submitted 28-Dec-2007)

Remarks: The chemistry, manufacturing and controls (CMC) section of this NDA has been referenced to the Treanda NDA 22-249 submitted by Cephalon on 19-Sep-2007 and approved on 20-Mar-2008. The CMC information remains the same except that the company has added 2.5% dextrose / 0.45% sodium chloride as a diluent (following reconstitution in vials using sterile water for injection) in addition to 0.9% sodium chloride which was approved in NDA 22-303.

In support of adding 2.5% dextrose / 0.45% sodium chloride, the company has submitted the results of a diluent compatibility study performed as part of the phase IV study under NDA 22-249 (submission dated 27-Aug-2008). The study was designed to examine the shelf life stability of Treanda[®] (bendamustine HCl for Injection in 100 mg and (b) (4) /vial dosages) following reconstitution in vials using sterile water for injection (SWFI) and after further dilution in IV bags of several commonly used diluents. These diluents were 0.9% sodium chloride (normal saline), (b) (4) solution, and 2.5% dextrose / 0.45% sodium chloride. Only the 2.5% dextrose/0.45% sodium chloride admixture showed similar bendamustine HCl (BM1) stability and purity when compared to a normal saline admixture. BM1 degradation was more rapid in both (b) (4) and (b) (4) than in normal saline. Hence 2.5% dextrose/0.45% sodium chloride solution could be substituted for 0.9% sodium chloride while maintaining acceptable stability (as specified in the package insert of NDA22-249).

The trademark was determined to be acceptable under NDA 22-249 review. The Office of Compliance issued an overall acceptable recommendation on 10-Oct-2008 (see attached report).

Conclusions and Recommendations:

Based on the review of additional compatibility data and the previous review of CMC information under NDA 22-249, this application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act.

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

/s/

Ravi Kasliwal
10/17/2008 08:22:38 AM
CHEMIST

Sarah Pope
10/17/2008 04:41:28 PM
CHEMIST

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22303/000
Org Code : 150
Priority : 1S

Sponsor: CEPHALON
NO CITY, , XX

Stamp Date : 31-DEC-2007
PDUFA Date : 31-OCT-2008
Action Goal :
District Goal: 01-SEP-2008

Brand Name : TREANDA
Estab. Name:
Generic Name: BENDAMUSTINE HYDROCHLORIDE
Dosage Form: (FOR INJECTION)
Strength : 100 MG/VIAL

FDA Contacts:	D. MESMER	Project Manager (HFD-800)	301-796-4023
	R. KASLIWAL	Review Chemist	301-796-1386
	S. POPE	Team Leader	301-796-1436

Overall Recommendation: ACCEPTABLE on 10-OCT-2008 by C. CRUZ (HFD-323) 301-796-3254

Establishment : (b) (4) FEI :

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-OCT-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : (b) (4) FEI : (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-OCT-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : (b) (4) FEI : (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22303/000	Action Goal:	
Stamp:	31-DEC-2007	District Goal:	01-SEP-2008
Regulatory Due:	31-OCT-2008	Brand Name:	TREANDA
Applicant:	CEPHALON	Estab. Name:	
	NO CITY, , XX	Generic Name:	BENDAMUSTINE
	1S		HYDROCHLORIDE
Priority:	150	Dosage Form:	(FOR INJECTION)
Org Code:		Strength:	100 MG/VIAL

Application Comment: THIS NDA WAS SUBMITTED FOR ADDITIONAL CLINICAL INDICATION AND THE CMC IS SAME AS IN NDA 22-249 FROM THE SAME COMPANY. THE CMC HAS BEEN REFERENCED TO NDA 22-249. (on 08-OCT-2008 by R. KASLIWAL () 301-796-1386)

FDA Contacts:	D. MESMER	(HFD-800)	301-796-4023	, Project Manager
	R. KASLIWAL		301-796-1386	, Review Chemist
	S. POPE		301-796-1436	, Team Leader

Overall Recommendation: ACCEPTABLE on 10-OCT-2008 by C. CRUZ (HFD-323) 301-796-3254

Establishment: (b) (4) FEI

DMF No: AADA:
R isibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Profile: SVL OAI Status: NONE

Estab. Comment: THIS FACILITY MANUFACTURES, (b) (4) ON
THE DRUG PRODUCT. (on 08-OCT-2008 by R. KASLIWAL () 301-796-1386)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-OCT-2008				KASLIWALR
SUBMITTED TO DO	08-OCT-2008	10D			ADAMSS
DO RECOMMENDATION	08-OCT-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
AC GMP EI 7/5/2007					
OC RECOMMENDATION	08-OCT-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: (b) (4) FEI (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: SVL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-OCT-2008				KASLIWALR
SUBMITTED TO DO	08-OCT-2008	GMP			ADAMSS
DO RECOMMENDATION	10-OCT-2008			ACCEPTABLE BASED ON FILE REVIEW	KCAMPBEL

Estab. Comment: (b) (4) ON DRUG

SUBSTANCE. (on 08-OCT-2008 by R. KASLIWAL () 301-796-1386)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-OCT-2008				KASLIWALR
SUBMITTED TO DO	08-OCT-2008	GMP			ADAMSS
DO RECOMMENDATION	08-OCT-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	08-OCT-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: (b) (4) FEI (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

LAST GMP EI OF 9/6-7/08 IS CLASSIFIED NAI. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION. PROFILE CLASS SVL WILL BE EVALUATED DURING THE NEXT SCHEDULED INSPECTION OF THIS FIRM.

CC RECOMMENDATION 10-OCT-2008

ACCEPTABLE CRUZC
BASED ON FILE REVIEW

THE DO RECOMMENDS ACCEPTABLE BASED ON FILE REVIEW.

Establishment:

(b) (4)

FEI

(b) (4)

DMF No:

AADA:

Responsibilities:

FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

Profile:

SVL

OAI Status:

NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
-----------------	------	------	------------	-------------------	---------

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC 08-OCT-2008

KASLIWALR

OC RECOMMENDATION 08-OCT-2008

ACCEPTABLE

ADAMSS

BASED ON PROFILE
