CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 17-422/S-047

Name: BiCNU® (Carmustine), powder for injection, 100 mg/vial

Sponsor: Emcure Pharmaceuticals Limited, India

Approval Date: June 13, 2014

This "Changes Being Effected in 30 days" supplemental new drug application proposes the addition of Emcure Pharmaceuticals Limited, India, as an alternate co-packaging site for BiCNU for Injection and Diluent (dehydrated alcohol Injection, USP).

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APPLICATION NUMBER:

NDA 17-422/S-047

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APPLICATION NUMBER:

NDA 17-422/S-047

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 17422/S-047

APPROVAL LETTER

Emcure Pharmaceuticals Limited, USA, US Agent for
Emcure Pharmaceuticals Limited, India
Attention: Pankaj Dave, PhD
Vice President, Regulatory Affairs
21B Cotters Lane
East Brunswick, New Jersey 08816

Dear Dr. Dave:

Please refer to your Supplemental New Drug Application (sNDA) dated December 13, 2013, received December 13, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BiCNU® (carmustine for injection), 100 mg/vial.

This "Changes Being Effected in 30 days" supplemental new drug application proposes the addition of Emcure Pharmaceuticals Limited, India as an alternate co-packaging site for BiCNU for Injection and Diluent (dehydrated alcohol Injection, USP).

We have completed our review of this supplemental new drug application. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Hasmukh Patel, Ph.D.
Branch Chief, Branch III
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

HASMUKH B PATEL
06/13/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-047

CHEMISTRY REVIEWS

QUALITY (CMC) REVIEW #**1**	1. ORGANIZATION ONDQA Div. 1, Branch 3 HFD-150	2. NDA NUMBER 017422

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Emcure Pharmaceuticals USA Inc. 21/B Cotters Lane East Brunswick, NJ 08816	**S047** (SDN 168) CBE-30 PDUFA Date: Jun. 13, 2014

5. PROPRIETARY	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
BiCNU®	Carmustine	N/A

8. COMMUNICATION PROVIDES FOR:

Addition of Emcure Pharmaceuticals Limited, India as an alternate co-packaging site for BiCNU for Injection and Diluent (Dehydrated Alcohol Injection, USP).

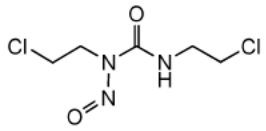
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Multiple Myeloma/Plasma Cell Disorders (8053006)	Rx only	N/A
12. DOSAGE FORM	13. POTENCY	
Lyophilized Powder, for Injection	100 mg	

14. CHEMICAL NAME AND STRUCTURE

1,3-bis(2-chloroethyl)-1-nitrosourea

CODE NAME:	BCNU, L01AD01
EMPIRICAL FORMULA:	$C_5H_9Cl_2N_3O_2$
MOLECULAR WEIGHT:	214.06
CASRN:	154-93-8

CHEMICAL STRUCTURE:



INDICATION:	For the chemotherapy of certain neoplastic diseases such as brain tumor, multiple myeloma, Hodgkin's disease, and non-Hodgikin's lymphomas.

15. COMMENT

The proposed site at Emcure Pharmaceuticals Limited in India for the co-packaging of finished drug product in a carton is an approved site for the manufacturing, testing, stability studies and packaging of each of the two DP vials—BiCNU and Diluent. A Master Batch Packaging Record is provided to support adequately the proposed co-packaging operation at Emcure Pharmaceuticals. There is no change to the approved co-packaging presentation, and no other changes beyond those proposed in this supplement.

The proposed change will not impact adversely the identity, strength, purity and quality of drug product.

16. CONCLUSION AND RECOMMENDATION

From the CMC perspective this supplement, as amended, is recommended for APPROVAL.

17. CMC REVIEWER	18. SIGNATURE	19. DATE COMPLETED
Huai T. (Ted) Chang, PhD	See appended electronic signature sheet	Jun. 10, 2014

REVIEW NOTES—CHEMISTRY, MANUFACTURING AND CONTROLS

BACKGROUND—DRUG SUBSTANCE AND DRUG PRODUCT

BiCNU® (carmustine for injection) is available in 100 mg single dose vials of sterile lyophilized material with an appearance of pale yellow flakes or congealed mass. The drug substance carmustine is highly soluble in alcohol and lipids, and poorly soluble in water. Sterile diluent—a vial containing 3 mL of Dehydrated Alcohol Injection, USP—is co-packaged with the active drug product in a carton. BiCNU should be stored in a refrigerator at 2-8°C (36-46°F).

Carmustine or BCNU (bis-chloroethylnitrosourea) is a mustard gas-related β-chloro-nitrosourea compound used as an alkylating agent in the chemotherapy of certain neoplastic diseases (for example brain tumor, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas). As a dialkylating agent, BCNU is able to form interstrand crosslinks in DNA, which prevents DNA replication and DNA transcription.

NDA 017422 for BiCNU® for Injection—a 505(b)(1) NME new drug application—was initially approved in the U.S. in 1977. BiCNU was initially owned by Bristol-Myers Squibb (BMS) Company until Jan. 2013 when it was transferred to Emcure Pharmaceuticals Limited. In India, carmustine is marketed under the brand name Carustine®.

PROPOSED CHANGE AND REVIEW

The purpose of this supplement is to add Emcure Pharmaceuticals Limited in India as a co-packaging site for the following items.

- BiCNU (Carmustine for injection, USP) in 100 mg/vial.
- Diluent (Dehydrated Alcohol Injection, USP)—3 mL in vial.

Currently approved co-package consists of one labeled vial of BiCNU and one labeled vial of diluent packed in a carton along with one leaflet. Co-packaging is performed as per Master Batch Packaging Record.

The proposed co-packaging site is the same facility where BiCNU (Carmustine for injection) and the Diluent (Dehydrated Alcohol Injection USP) are manufactured. This facility was last inspected by FDA on Apr. 22–26, 2013 and found to be in compliance.

Proposed Co-packaging Site
Emcure Pharmaceuticals Limited Plot No. P-1 & P-2, I.T.B.T. Park Phase-II, MIDC, Hinjwadi Pune, Maharashtra 00041-1057 INDIA FEI number 3005151215 DUNS number 862602830
Currently approved for the manufacturing, testing, stability studies and packaging of BiCNU and Diluent.

CMC Review Note: S045 was approved in Sep. 2013 to manufacture Diluent at Emcure Pharmaceuticals Limited in India. The vial-stopper-seal container closure system for the Diluent

is USP-compliant. The vial-stopper-seal system was the originally approved container closure system before it was changed to flame-sealed 5 mL ampule Type I glass at Luitpold (S037 in 2007).

ESTABLISHMENT EVALUATION

The proposed co-packaging site—Emcure Pharmaceuticals Limited in India—has received an overall recommendation of ACCEPTABLE from the Office of Compliance (OC).

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 17422/047	**Sponsor:**	EMCURE PHARMS LTD
Org. Code:	161		21B COTTERS LANE
Priority:	1S		EAST BRUNSWICK, NJ 08816
Stamp Date:	13-DEC-2013	**Brand Name:**	BICNU
PDUFA Date:	13-JUN-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	CARMUSTINE
District Goal:	09-MAY-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR INJECTION SOLUTION; CARMUSTINE; 100MG/VIAL

FDA Contacts:	H. CHANG	Prod Qual Reviewer		3017961974
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	T. CARIOTI	Regulatory Project Mgr		3017962848
	N. CHIDAMBARAM	Team Leader		3017961339

Overall Recommendation:	ACCEPTABLE	on 19-MAY-2014	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 25-MAR-2014	by EES_PROD		
	ACCEPTABLE	on 13-MAR-2014	by EES_PROD		
	PENDING	on 15-JAN-2014	by EES_PROD		
	PENDING	on 20-DEC-2013	by EES_PROD		

Establishment:	**CFN:** **FEI:** 3005151215		
	EMCURE PHARMACEUTICALS LIMITED PL P1/P2,ITBT PARK, PHASE II		
	HINJWADI, PUNE, MAHARASHTRA, INDIA		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-MAY-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

CMC ASSESSMENT, CONCLUSION AND RECOMMENDATION

The proposed site at Emcure Pharmaceuticals Limited in India for the co-packaging of finished drug product in a carton is an approved site for the manufacturing, testing, stability studies and packaging of each of the two DP vials—BiCNU and Diluent. A Master Batch Packaging Record (dated May 2013) is provided to support adequately the proposed co-packaging operation at Emcure Pharmaceuticals Limited. There is no change to the approved co-packaging presentation, and no other changes beyond those proposed in this supplement.

The proposed change will not impact adversely the identity, strength, purity and quality of drug product. From the CMC perspective this supplemental application, as amended, is recommended for APPROVAL.

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/s/

HUAI T CHANG
06/10/2014

HASMUKH B PATEL
06/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-047

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 17422/S-047

CBE SUPPLEMENT – ACKNOWLEDGEMENT

Emcure Pharmaceuticals Limited, USA, US Agent for
Emcure Pharmaceuticals Limited, India
Attention: Pankaj Dave, PhD
Vice President, Regulatory Affairs
21B Cotters Lane
East Brunswick, New Jersey 08816

Dear Dr. Dave:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 17422

SUPPLEMENT NUMBER: 047

PRODUCT NAME: BiCNU® (Carmustine, powder for injection 100 mg/vial)

DATE OF SUBMISSION: December 13, 2013

DATE OF RECEIPT: December 13, 2013

This supplemental application, submitted as a "Changes Being Effected in 30 Days" supplement, proposes the following change: inclusion of Emcure Pharmaceuticals Limited, India as a co-packaging site for BiCNU (Carmustine for injection, USP 100mg/vial) and Diluent (Dehydrated Alcohol Injection USP).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 11, 2014, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be June 13, 2014.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

JEWELL D MARTIN
12/20/2013