

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-137**

**CHEMISTRY REVIEW(S)**

**OFFICE ON NEW DRUG QUALITY ASSESSMENT**  
**DIVISION OF POST-MARKETING EVALUATION, BRANCH VIII**  
Review of Chemistry, Manufacturing, and Controls  
for the Division of Oncology Drug Products, HFD-150

**NDA #:** 22-137      **CHEM.REVIEW #:** 1      **REVIEW DATE:** 13-AUG-2008

<b><u>SUBMISSION/TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
NDA 22-137/SCM-002	12-DEC-2007	13-DEC-2007	22-FEB-2008

**NAME & ADDRESS OF APPLICANT:** Ebewe Pharma Ges. M.b.H. Nfg. KG  
Mondseestrasse 11  
4866 Unterach  
Austria

U.S. Agent:  
Ebewe Parenta Pharmaceuticals  
Three Southern Court  
West Columbia, SC 29169  
Linda Valentine  
Regulatory Affairs Manager  
(803) 461-5519

**DRUG PRODUCT NAME**

<u>Proprietary:</u>	N/A
<u>Nonproprietary/USAN:</u>	Fludarabine Phosphate Injection
<u>Code Names/#'s:</u>	N/A
<u>Chemical Type/</u>	5, New Manufacturer
<u>Therapeutic Class:</u>	S, Standard Review Drug

**ANDA Suitability Petition/DESI/Patent Status:** N/A

**PHARMACOLOGICAL**

**CATEGORY/INDICATION:** Fludarabine Phosphate Injection is a nucleotide metabolic inhibitor indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. Benefit in treatment-naïve or non-refractory CLL patients is not established.

<b><u>DOSAGE FORM:</u></b>	Solution, injectable
<b><u>STRENGTHS:</u></b>	25mg/mL
<b><u>ROUTE OF ADMINISTRATION:</u></b>	Injection
<b><u>DISPENSED:</u></b>	<u> X </u> Rx <u>  </u> OTC

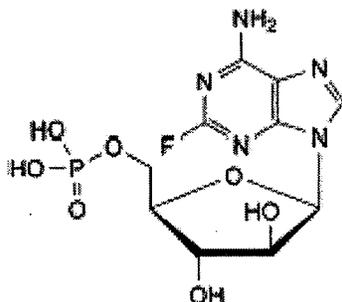
NDA 22-137 / SCM-002  
Fludarabine Phosphate Injection, 25mg/mL  
Ebewe Pharmaceuticals, Inc.

Page 2 of 5

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,**

**MOL.WT:**

9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl),  
or  
2-fluoro-ara-AMP



Molecular Formula: C<sub>10</sub>H<sub>13</sub>FN<sub>5</sub>O<sub>7</sub>P  
Molecular Weight: 365.2  
CAS No.: [75607-67-9]  
NDC: 68842-007-01; 50 mg/2 mL (25 mg/mL)

**SUPPORTING DOCUMENTS:** None

**REMARKS/COMMENTS:**

This "Supplement - Changes Being Effected" (CBE-0) submission provides for adding additional contract testing laboratories. These facilities will perform testing of drug substance, excipients, drug product and packaging components. In addition, a facility currently used for sterility and bacterial endotoxins testing will also conduct testing of drug substance, excipients, drug product and packaging components. An EES Request was submitted for the new facilities on 23-JAN-2008. The Office of Compliance inspected one facility on 07-JUL-2008, the facilities were judged acceptable and a recommendation for approval was issued 12-AUG-2008, signed by S. Adams, HFD-325.

**CONCLUSIONS & RECOMMENDATIONS:**

**APPROVAL**

The information submitted in the supplement supports the proposed changes. Approval is recommended.

*(see attached electronic signature page)*

---

Joel S. Hathaway, Ph.D.  
Reviewing Chemist

**NDA 22-137 / SCM-002**  
**Fludarabine Phosphate Injection, 25mg/mL**  
**Ebewe Pharmaceuticals, Inc.**

**Page 3 of 5**

cc: Orig. NDA 22-137  
OND/DODP/Division File (HFD-150)  
ONDQA/DPE/Chem/JS Hathaway  
ONDQA/DPE/ChemPAL/LZhou  
ONDQA/DPE/ChemBranchChf/HPatel  
ONDQA/DPE/ProjMgr/

**filename:** C:\Documents and Settings\hathaways\My Documents\MSWordDocs\NDA  
Reviews\SuppNDAs\22137\N22137r.scm.002.doc

**Approval**

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**CHEMISTRY REVIEW NOTES AND ASSESSMENTS**

**I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data**  
**P DRUG PRODUCT**  
**P.3 Manufacture**  
*P.3.1 Manufacturers*

The submission provides for adding additional contract testing laboratories. These facilities will perform testing of drug substance, excipients, drug product and packaging components. In addition, a facility currently used for sterility and bacterial endotoxins testing will also conduct testing of drug substance, excipients, drug product and packaging components. The new facilities were identified:

\_\_\_\_\_

**b(4)**

FEI: \_\_\_\_\_

and

\_\_\_\_\_

**b(4)**

FEI: \_\_\_\_\_

The current cGMP certifications of these facilities were provided in the supplemental application.

The currently approved facility with expanded functions is identified as:

\_\_\_\_\_

**b(4)**

**Reviewer Evaluation:** An EES Request was submitted for the new facilities on 23-JAN-2008. The Office of Compliance inspected one facility on 07-JUL-2008, issuing a Form 483; after the firm's response, the facilities were judged acceptable and a recommendation

**NDA 22-137 / SCM-002**

**Page 5 of 5**

**Fludarabine Phosphate Injection, 25mg/mL**

**Ebewe Pharmaceuticals, Inc.**

for approval was issued 12-AUG-2008, signed by S. Adams, HFD-325. Acceptable.

**III. List of Comments/Deficiencies to be Communicated to Holder**

None.

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/s/  
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Steve Hathaway  
8/13/2008 01:36:47 PM  
CHEMIST  
Additional testing facilities  
For your concurrence

Hasmukh Patel  
8/13/2008 01:38:45 PM  
CHEMIST

**OFFICE ON NEW DRUG QUALITY ASSESSMENT**  
**DIVISION OF POST-MARKETING EVALUATION, BRANCH VIII**  
Review of Chemistry, Manufacturing, and Controls  
for the Division of Oncology Drug Products, HFD-150

**NDA #:** 22-137      **CHEM.REVIEW #:** 1      **REVIEW DATE:** 05-JUN-2008

<b><u>SUBMISSION/TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
NDA 22-137/SCS-001	11-DEC-2007	12-DEC-2007	22-FEB-2008

**NAME & ADDRESS OF APPLICANT:** Ebewe Pharma Ges. M.b.H. Nfg. KG  
Mondseestrasse 11  
4866 Unterach  
Austria

U.S. Agent:  
Ebewe Parenta Pharmaceuticals  
Three Southern Court  
West Columbia, SC 29169  
Linda Valentine  
Regulatory Affairs Manager  
(803) 461-5519

**DRUG PRODUCT NAME**

<u>Proprietary:</u>	N/A
<u>Nonproprietary/USAN:</u>	Fludarabine Phosphate Injection
<u>Code Names/ #'s:</u>	N/A
<u>Chemical Type/</u>	5, New Manufacturer
<u>Therapeutic Class:</u>	S, Standard Review Drug

**ANDA Suitability Petition/DESI/Patent Status:** N/A

**PHARMACOLOGICAL**

**CATEGORY/INDICATION:** Fludarabine Phosphate Injection is a nucleotide metabolic inhibitor indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. Benefit in treatment-naïve or non-refractory CLL patients is not established.

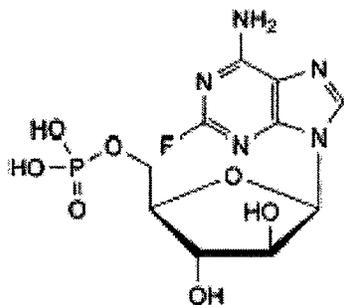
<b><u>DOSAGE FORM:</u></b>	Solution, injectable
<b><u>STRENGTHS:</u></b>	25mg/mL
<b><u>ROUTE OF ADMINISTRATION:</u></b>	Injection
<b><u>DISPENSED:</u></b>	<u> X </u> Rx <u>    </u> OTC

Fludarabine Phosphate Injection, 25mg/mL  
Ebewe Pharmaceuticals, Inc.

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,**

**MOL.WT:**

9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl),  
or  
2-fluoro-ara-AMP



Molecular Formula: C<sub>10</sub>H<sub>13</sub>FN<sub>5</sub>O<sub>7</sub>P  
 Molecular Weight: 365.2  
 CAS No.: [75607-67-9]  
 NDC: 68842-007-01; 50 mg/2 mL (25 mg/mL)

**SUPPORTING DOCUMENTS:** None

**REMARKS/COMMENTS:**

This "Supplement - Changes Being Effected" (CBE-0) submission provides for a change in \_\_\_\_\_ from not more than \_\_\_\_\_, and for a change to the \_\_\_\_\_ from \_\_\_\_\_. The Master Batch Compounding Record (MBR) was revised to reflect these changes, along with the option for a \_\_\_\_\_, a new item number \_\_\_\_\_ for active ingredient to be used in product manufactured for the U.S. market and a corresponding MBR document number \_\_\_\_\_ a new item number for Sodium Hydroxide \_\_\_\_\_ used in the USA-product manufacturing process, a new document number \_\_\_\_\_, a new item number \_\_\_\_\_ for finished product manufactured for the U.S. market, minor changes to \_\_\_\_\_ corrections of typographic errors, and the addition of the previously approved \_\_\_\_\_

b(4)

A description of the manufacturing process and process controls, including control of critical steps and intermediates, was provided, along with the revised MBR and \_\_\_\_\_ Data from a \_\_\_\_\_ was provided to validate the \_\_\_\_\_

NDA 22-137 / SCS-001  
Fludarabine Phosphate Injection, 25mg/mL  
Ebewe Pharmaceuticals, Inc.

Page 3 of 6

A Microbiology Consultation Request was sent 23-JAN-2008, and returned as NAI on 21-MAR-2008, with the comment, "Acceptable \_\_\_\_\_ negative after incubation. Media supports growth. Environmental monitoring yielded no growth. Total filling time was \_\_\_\_\_ Acceptable."

b(4)

**CONCLUSIONS & RECOMMENDATIONS:**

**APPROVAL**

The information and data submitted in the supplement support the proposed changes. Approval is recommended.

*(see attached electronic signature page)*

---

Joel S. Hathaway, Ph.D.  
Reviewing Chemist

cc: Orig. NDA 22-137  
OND/DODP/Division File (HFD-150)  
ONDQA/DPE/Chem/JSHathaway  
ONDQA/DPE/ChemPAL/LZhou  
ONDQA/DPE/ChemBranchChf/HPatel  
ONDQA/DPE/ProjMgr/

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**Approval**

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**CHEMISTRY REVIEW NOTES AND ASSESSMENTS**

**I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data  
P DRUG PRODUCT  
P.3 Manufacture  
P.3.2 Batch Formula**

The Master Batch Compounding Record (MBR) was revised to incorporate the option for a \_\_\_\_\_ **b(4)**

**Reviewer Evaluation:** Acceptable.

**P.3.3 Description of Manufacturing Process and Process Controls  
P.3.4 Controls of Critical Steps and Intermediates**

The manufacturing process and in-process controls have not been fundamentally changed. The Master Batch Compounding Record (MBR) and \_\_\_\_\_ were revised to reflect the proposed changes, along with new document and item numbers for compounding components and product manufactured for the U.S. market. Minor changes to \_\_\_\_\_, corrections of typographic errors, and the addition of the previously approved \_\_\_\_\_ were also incorporated. **b(4)**

The proposed German and English-translation MBR and \_\_\_\_\_ documents were provided.

**Reviewer Evaluation:** Acceptable.

**P.3.5 Process Validation and/or Evaluation**

A media fill batch was produced and evaluated for microbiological quality performance of the extended fill period \_\_\_\_\_. A Microbiology Consultation Request was sent 23-JAN-2008, and returned as NAI on 21-MAR-2008, with the comment, "Acceptable \_\_\_\_\_, negative after incubation. Media supports growth. Environmental monitoring yielded no growth. Total filling time was \_\_\_\_\_." **b(4)**  
\_\_\_\_\_ Acceptable."

**Reviewer Evaluation:** Acceptable.

**P.7 Container Closure System**

The \_\_\_\_\_ from \_\_\_\_\_ **b(4)**  
\_\_\_\_\_ The manufacturer, composition and dimensions of the new cap remain the

**NDA 22-137 / SCS-001**  
**Fludarabine Phosphate Injection, 25mg/mL**  
**Ebewe Pharmaceuticals, Inc.**

**Page 5 of 6**

same. The ~~\_\_\_\_\_~~ is not a product-contacting packaging component.

**b(4)**

**Reviewer Evaluation:** Acceptable.

**III. List of Comments/Deficiencies to be Communicated to Holder**

None.

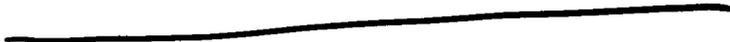
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**NDA 22-137 / SCS-001**  
**Fludarabine Phosphate Injection, 25mg/mL**  
**Ebewe Pharmaceuticals, Inc.**

**Page 6 of 6**

NDA XX-XXX

DRAFT OF CHEMIST'S LETTER TO FIRM



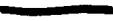
**b(4)**

Joel S. Hathaway, Ph. D.  
Review Chemist

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/s/

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Steve Hathaway  
6/12/2008 12:45:30 PM  
CHEMIST  
Filling time limits  AP recommended  
For your concurrence

b(4)

Liang Zhou  
6/12/2008 12:47:59 PM  
CHEMIST  
for BC, Dr. H . Patel



**NDA 22-137**

**Fludarabine Phosphate Injection**

**EBEWE Pharma GES. M.b.H. Nfg. KG.**

**Mark Sassaman, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of Premarketing Assessment and Manufacturing  
Science (Branch V)**

**for**

**The Division of Drug Oncology Products (HFD-150)**



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# Chemistry Review Data Sheet

1. NDA 22-137
2. REVIEW #1
3. REVIEW DATE: 11 SEP 2007
4. REVIEWER: Mark Sassaman, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents  
Original Application

Document Date  
24 NOV 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed  
Original Application  
BC Amendment

Document Date  
24 NOV 2006  
30 MAR 2007

7. NAME & ADDRESS OF APPLICANT:

Establishment Information:

Name: EBEWE Pharma Ges. M.b.H. Nfg. KG  
Mondseestrasse 11  
Address: 4866 Unterach  
AUSTRIA  
Representative: Dr. Friederich Hillebrand, General Manager  
Telephone: +43-7665-8123-0



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### United States Agent Information:

Name: B&H Consulting Services, Inc.  
 Address: 55 North Gaston Avenue  
 Somerville NJ 08876  
 Representative: Elizabeth N. Dupras, RAC; Project Manager  
 Telephone: (908)704-1691 ext. 223

### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Fludarabine Phosphate Injection
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3, 5
  - Submission Priority: S

### 9. LEGAL BASIS FOR SUBMISSION:

FDC Act	505(b)(2)
RLD	Fludara® (Fludarabine Phosphate) for Injection
Dosage Form	Lyophilized solid cake to prepare injectable
Strength	50 mg/vial; 25 mg/mL after reconstitution
RLD NDA	20-038
NDA Holder	Berlex Laboratories

NDA 22-137 was filed under section 505(b)(2) of the Federal Food Drug and Cosmetic Act rather than 505 (j) due to the change in formulation with respect to previously approved products. The new formulation

b(4)

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10. PHARMACOL. CATEGORY: Antineoplastic; Nucleotide Metabolic Inhibitor

11. DOSAGE FORM: INJ SOL (Injection, solution)

12. STRENGTH/POTENCY: 25 mg/mL (50 mg/2 mL vial)

13. ROUTE OF ADMINISTRATION: Intravenous injection

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s)	
2-Fluoro-9-(β-D-arabinofuranosyl)adenine-5'-phosphate	
2-Fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)-9H-purin-6-amine	
[(2R,3R,4R,5R)-2-(6-Amino-2-fluoro-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl] methyl phosphate	
9-β-D-Arabinofuranosyl-2-fluoroadenine-5'-(dihydrogen phosphate)	
2-Fluoro- <i>ara</i> -AMP	
Empirical Formula	C <sub>10</sub> H <sub>13</sub> FN <sub>5</sub> O <sub>7</sub> P
Molecular Weight	365.21
CAS Registry Number	[75607-67-9] (Fludarabine Phosphate); [21679-14-1] (Fludarabine)
Structural Formula	

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
[REDACTED]	II	[REDACTED]	[REDACTED]	1	Adequate	15 FEB 2007	Supporting documents need translation (Italian)
	II			1	Adequate	30 MAY 2007	Translations provided for supporting documents
	II			1	Adequate	27 FEB 2007	
	III			1	Adequate	07 MAR 2007	
	III			1	Adequate	23 MAR 2007	
	III			1	Adequate	12 APR 2007	
	III			1	Adequate	23 MAR 2007	
	V			7	N/A		Microbiology Review Bryan Riley

<sup>1</sup> Action codes for DMF Table:

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows:
- 2 – Type I DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

b(4)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NONE		

### 18. STATUS:

#### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	29 JAN 2007	Office of Compliance
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS	Revisions recommended (see DFS for document)	30 APR 2007	Kellie Taylor, Pharm. D.
DDMAC	Recommendations made (see DFS for document)	30 JAN 2007	Joseph A. Grillo, Pharm. D.
EA	Categorical Exclusion Claim under 21 CFR 25.31(a)-ACCEPTABLE	22 FEB 2007	Mark Sassaman, Ph.D.
Microbiology	Recommended for Approval	28 JUN 2007	Bryan S. Riley, Ph.D.

#### OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:



## Executive Summary Section

five milligrams per square meter infused over thirty minutes on five consecutive days. **b(4)**  
Treatment is repeated monthly \_\_\_\_\_

**C. Basis for Approvability or Not-Approval Recommendation**

EBEWE's proposed drug product, Fludarabine Phosphate Injection, differs from previous formulations in two respects. \_\_\_\_\_

\_\_\_\_\_ **b(4)**  
\_\_\_\_\_ During formulation development, EBEWE carefully studied the impact of pH on degradation of the dissolved drug substance as well as the pH dependent solubility of the drug substance. The current formulation represents an optimization of both parameters.

Stability studies have been conducted under the recommended storage conditions for eighteen months. Linear regression analyses of two parameters, Fludarabine Phosphate content and the appearance of a degradation product \_\_\_\_\_ **b(4)**  
predict that both will be maintained within specifications for the proposed expiration period of thirty-six months. The applicant has committed to continue monitoring stability through the proposed expiration period per their primary stability protocol.

Fludarabine Phosphate has been marketed in the United States for sixteen years. It is the subject of two monographs in the United States Pharmacopoeia and one in the European Pharmacopoeia. The applicant makes extensive use of testing methods and specifications from these compendial sources.

**III. Administrative****A. Reviewer's Signature**

\_\_\_\_\_  
Mark Sassaman, Ph.D. 11 SEP 2007

\_\_\_\_\_  
Richard T. Lostritto, Ph.D. 11 SEP 2007

**B. Endorsement Block**

Chemist: Mark Sassaman, Ph.D./Date: 11 SEP 2007  
Pharmaceutical Assessment Lead: Sarah Pope, Ph.D./Date:  
Division Director: Richard T. Lostritto, Ph.D./Date:  
Project Manager: Tammie Brent-Steele/Date:

**C. CC Block**

Tammie Brent-Steele, Sarah Pope, Karl Stiller

64 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Mark Sassaman  
9/17/2007 10:47:13 AM  
CHEMIST

Richard Lostritto  
9/17/2007 11:15:09 AM  
CHEMIST

**Initial Quality Assessment  
Branch V  
Pre-Marketing Assessment and Manufacturing Science Division III  
Office of New Drug Quality Assessment**

OND Division:	Division of Drug Oncology Products
NDA:	22-137
Applicant:	Ebewe Pharma
Stamp date:	24-NOV-2006
PDUFA Date:	24-SEP-2007
Proposed Trade Name:	Fludarabine phosphate injection
Established Name:	Fludarabine phosphate
Laboratory Code:	N/A
Dosage Form:	Sterile solution
Route of Administration:	Intravenous
Indication:	Treatment of B-cell chronic lymphocytic leukemia.

Pharmaceutical Assessment Lead: Sarah C. Pope, Ph.D.

	YES	NO
ONDQA Fileability:	<u>√</u>	—
Draft Comments for 74-Day Letter:	<u>√</u>	—

## Summary, Critical Issues and Comments

### A. Summaries

#### Background Summary

NDA 22-137 is submitted under Section 505(b)(2) for Fludarabine phosphate injection, 25 mg/mL, intended for treatment of chronic lymphocytic leukemia. The reference listed drug is Fludara® (fludarabine phosphate) for injection, as approved under NDA 20-038.

The basis for NDA 22-137 is a formulation revision to the reference listed drug Fludara (fludarabine phosphate) for injection. The approved and proposed products share the same active ingredient, route of administration, and general dosing regimen. However, Fludara is marketed as a lyophilized powder for reconstitution while the currently proposed product will be marketed as a solution (25 mg/mL) for dilution and intravenous administration. The proposed solution formulation also contains disodium hydrogen phosphate dihydrate as an additional ingredient.

#### Drug Substance Summary

Fludarabine phosphate is a white

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b(4)

attached to the primary (5') carbon (Figure 1).

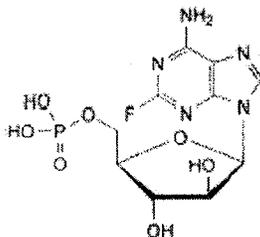


Figure 1. Fludarabine phosphate (MW=365.21 g/mole)

All Chemistry, Manufacturing and Controls information for fludarabine phosphate is cross-referenced to DMFs

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b(4)

The Sponsor has proposed a 

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 retest period when stored at 2-8°C, for the drug substance as manufactured by both proposed suppliers.

#### Drug Product Summary

Fludarabine phosphate injection is formulated as a 25 mg/mL (50 mg/vial) sterile solution. The

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b(4)

\_\_\_\_\_ The final drug product is tested for description, clarity of solution, color of solution, visible particulates, subvisible particulates, extractable volume, pH, density, identification (HPLC and UV-Vis), strength (HPLC), chromatographic purity (HPLC), sterility (USP <71>), and bacterial endotoxins (USP <85>). Fludarabine phosphate injection is packaged into glass vials \_\_\_\_\_

b(4)

The proposed manufacturing sites are listed below:

Manufacturing  
Ebewe Pharma Ges.m.b.H. Nfg.KG  
Mondseestraße 11  
4866 Unterach  
Austria  
FEI# 3002829723

\_\_\_\_\_ b(4)

The Sponsor provides long term ( $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ ; 9 months) and room temperature ( $25^{\circ}\text{C} \pm 3^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ , 6 months) stability data for four exhibit batches of fludarabine phosphate injection, when stored \_\_\_\_\_  
\_\_\_\_\_ Photostability conditions were studied using one of the primary stability batches.

b(4)

The Sponsor proposes a 36-month expiration dating period for the concentrate, when stored under refrigerated conditions \_\_\_\_\_

## B. Critical issues for review and recommendation

### Drug Substance

- a. The Sponsor proposes revisions to the current compendial specifications for impurities for fludarabine phosphate. These revisions should be assessed in relation to qualified levels as well as potential stability considerations.
- b. In the administrative section, the Sponsor mentions two separate DMFs for fludarabine phosphate \_\_\_\_\_ Acceptable letters of authorization are provided for both DMFs, and separate sections are provided in the Quality Overall Summary. However, the intention for the second DMF reference is unclear and should be confirmed as part of the CMC review. The manufacturing origin of the drug substance utilized for primary stability studies should be confirmed immediately upon review commencement. \_\_\_\_\_
- c. All Chemistry, Manufacturing and Controls information for fludarabine phosphate is cross-referenced to \_\_\_\_\_ Both DMFs should be assessed for their acceptability to support this proposed NDA, as applicable.

b(4)

b(4)

**Drug Product**

- a. The revision of the currently approved lyophilized formulation (Fludara) to that of a solution for dilution and intravenous administration presents potential new issues related to stability and impurity profiles for the dissolved drug substance. These issues should be carefully assessed during the CMC review, in order to confirm that the proposed solution formulation is sufficiently stable and pure for its intended storage and usage conditions.
- b. Updated stability data should be submitted to support the proposed expiration dating period of 36 months.
- d. The manufacturing process used to manufacture primary stability batches should be confirmed as representative of that proposed for commercial supplies.

**C. Comments for 74-day Letter:**

1. Updated stability data should be provided as soon as possible, for the drug product. Stability updates should be submitted in SAS transport files and should include statistical analysis of all stability-indicating parameters.

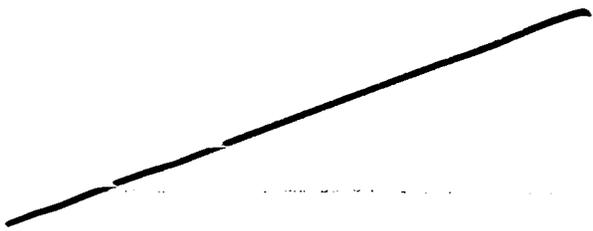
**Appears This Way  
On Original**

**D. Recommendation for fileability: Fileable**

**Fileability Template**

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	Data have been provided but without analysis. Additional data should be provided in a timely update.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √		<b>Microbiology</b> Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CBER LNC DMETS/ODS <b>EER</b>
		√		

Have all DMF References been identified? Yes (✓) No ( )

DMF Number	Holder	Description	LOA Included
			Yes
			Yes
			Yes
			Yes

b(4)

**Recommendation for Team Review:**

This NDA does not contain a significant amount of CMC information, due to the straightforward nature of the dosage form as well as the cross-referenced drug substance information. This review should be easily conducted by a single reviewer, and the team approach is not recommended for this NDA.

**Appears This Way  
On Original**

Sarah C. Pope, Ph.D.  
Pharmaceutical Assessment Lead

18-JAN-2007  
Date

Ravi Harapanhalli, Ph.D.  
Branch Chief

18-JAN-2007  
Date

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

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Sarah Pope  
1/18/2007 05:43:47 PM  
CHEMIST

Ravi Harapanhalli  
1/18/2007 07:44:00 PM  
CHEMIST