

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-137

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EBEWE Pharma



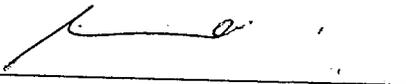
Patent Certification

According to the information in the Food and Drug Administration Orange Book Database (<http://www.fda.gov/cder/ob/docs/queryai.htm>), there are no unexpired patents for fludarabine phosphate as of 10 October 2006.

In accordance with 21 CFR 314.94(a)(12)], EBEWE Pharma Ges.m.b.H. Nfg.KG presents the following certification.

NO RELEVANT PATENTS CERTIFICATION:

In accordance with 21 CFR 314.94(a)(12)(i)(2), EBEWE Pharma Ges.m.b.H. Nfg.KG certifies that, to the best of its knowledge, there are no unexpired patents for fludarabine phosphate as of 10 October 2006.



Dr. Michael Mussill
Head of Regulatory Affairs
EBEWE Pharma Ges.m.b.H. Nfg.KG

15 Nov 2006
Date



Patent Certification

According to the information in the Food and Drug Administration Orange Book Database (<http://www.fda.gov/cder/ob/docs/queryai.htm>), there are no unexpired patents for fludarabine phosphate as of 19 September 2007.

In accordance with 21 CFR 314.50(i)(1)(i)(A)(2), EBEWE Pharma Ges.m.b.H. Nfg.KG presents the following certification.

PARAGRAPH II CERTIFICATION:

In accordance with 21 CFR 314.50(i)(1)(i)(A)(2), EBEWE Pharma Ges.m.b.H. Nfg.KG certifies that, to the best of its knowledge, there are no unexpired patents for fludarabine phosphate as of 19 September 2007.

Dr. R. Gmeinbauer
Head of Regulatory Affairs / New Products
EBEWE Pharma Ges.m.b.H. Nfg.KG

19 Sept 2007

Date

EBEWE Pharma



Exclusivity Statement

According to the information in the Food and Drug Administration Orange Book Database, there is no unexpired exclusivity for fludarabine phosphate as of 10 October 2006.

Based upon the Patent Certification and Exclusivity Statement contained in this application, EBEWE Pharma Ges.m.b.H. Nfg.KG intends to market Fludarabine Phosphate Injection upon approval of this application.

A handwritten signature in black ink, appearing to read "Michael Mussill", written over a horizontal line.

Dr. Michael Mussill
Head of Regulatory Affairs
EBEWE Pharma Ges.m.b.H. Nfg.KG

15 Nov 2006
Date

EXCLUSIVITY SUMMARY

NDA # 22-137

SUPPL #

HFD # 150

Trade Name

Generic Name Fludarabine Phosphate Injection

Applicant Name EBEWE

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

no studies were performed

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-038

Fludara

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Dotti Pease for Tammie Brent
Title: Project Manager
Date: 9-19-07

Name of Office/Division Director signing form: Ann Farrell, M.D.
Title: Deputy Director, DDOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Ann Farrell
9/21/2007 02:35:41 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-137 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 11-24-06 PDUFA Goal Date: 9-24-07

HFD 150 Trade and generic names/dosage form: Fludarabine Phosphate Injection 25mg/ml

Applicant: EBEWE Pharma Therapeutic Class: _____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): _____

Indication #1: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-137

Page 3

This page was completed by:

{See appended electronic signature page}

**Tammie Brent, RN, MSN
Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Tammie Brent, RN, MSN
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Tammie Brent-Steele
2/2/2007 04:34:12 PM

EBEWE Pharma



Debarment Certification and List of Convictions

EBEWE Pharma Ges.m.b.H. Nfg.KG hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

EBEWE Pharma Ges.m.b.H. Nfg.KG hereby certifies that it did not and will not use in any capacity the services of any person convicted under section 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in black ink, appearing to read "M. Mussill", is written over a horizontal line.

Dr. M. Mussill
Head of Regulatory Affairs
EBEWE Pharma Ges.m.b.H. Nfg.KG

15 Nov 2006

Date

A handwritten signature in black ink, appearing to read "Elizabeth N. Dupras", is written over a horizontal line.

Elizabeth N. Dupras, RAC
Project Manager
B&H Consulting Services, Inc.
US Agent for EBEWE Pharma Ges.m.b.H. Nfg.KG

20 Nov 06

Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

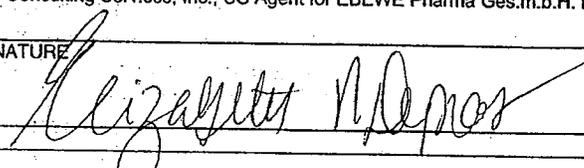
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	NO CLINICAL STUDIES SUBMITTED IN NDA 22-137	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Elizabeth N. Dupras	TITLE Senior Project Manager
FIRM/ORGANIZATION B&H Consulting Services, Inc.; US Agent for EBEWE Pharma Ges.m.b.H. Nfg.KG	
SIGNATURE 	DATE 25 January 2007

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

EBEWE Pharma



Financial Certification-Disclosure Statement

EBEWE Pharma Ges.m.b.H. Nfg.KG has requested a waiver of the requirement to conduct a bioequivalence study in accordance with 21 CFR 320.22(b)(1).

In accordance with this waiver request, EBEWE Pharma Ges.m.b.H. Nfg.KG declares that they neither contracted with one or more clinical investigators to conduct studies nor submitted studies conducted by others under contract to the applicant.

A handwritten signature in black ink, appearing to read "F. Hillebrand", written over a horizontal line.

Dr. Friedrich Hillebrand
General Manager
EBEWE Pharma Ges.m.b.H. Nfg.KG

15 Nov 2006
Date

Pease, Dorothy W

From: Dupras, Beth [edupras@bhconsultingservices.com]
Sent: Wednesday, September 19, 2007 8:41 AM
To: Pease, Dorothy W; Brent-Steele, Tammie
Cc: Ribbans, Helen
Subject: RE: NDA 22-137: Response to Labeling Deficiencies
Attachments: NDA 22-137-Revised FPI-19Sep07.doc; NDA 22-137-Revised FPI-19Sep07-TRK CHGS.doc

Thank you, Dottie!

Yesterday, Tammie and I discussed some minor corrections to cross-references and "fludarabine" vs. "fludarabine phosphate". Therefore, attached please find the "final" version, which may differ slightly from the version Tammie provided yesterday. I have also attached a "track changes" version so you can easily see that the changes were incorporated.

Do not hesitate to contact me if you have any questions/concerns!

Best regards,
Beth

Elizabeth N. Dupras, RAC
Senior Project Manager
B&H Consulting Services, Inc.
908-704-1691 x223
908-704-1693 (fax)
edupras@bhconsultingservices.com

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From: Pease, Dorothy W [mailto:dorothy.pease@fda.hhs.gov]
Sent: Wednesday, September 19, 2007 8:29 AM
To: Dupras, Beth; Brent-Steele, Tammie
Cc: Ribbans, Helen
Subject: RE: NDA 22-137: Response to Labeling Deficiencies

b(4)

Also, it's not necessary for you to send me another version of the labeling as I will be attaching the FDA version to the letter. I just need to know if you agree and what changes you are making.

Thanks

Dotti

From: Dupras, Beth [mailto:edupras@bhconsultingservices.com]

9/21/2007

Sent: Tuesday, September 18, 2007 4:09 PM
To: Brent-Steele, Tammie
Cc: Pease, Dorothy W; Ribbans, Helen
Subject: RE: NDA 22-137: Response to Labeling Deficiencies

Thanks Tammie,
I don't think there will be any problem accepting these changes; however, I will need to forward to EBEWE in Austria. I will most likely submit the revised labeling tomorrow. I will e-mail the submission to Dotti, as well.

Thanks again!
Beth

From: Brent-Steele, Tammie [mailto:tammie.brentsteele@fda.hhs.gov]
Sent: Tuesday, September 18, 2007 4:01 PM
To: Dupras, Beth
Cc: Pease, Dorothy W
Subject: RE: NDA 22-137: Response to Labeling Deficiencies

Hi Beth,

The team was fine with the vial and carton label. We have some revisions of the package insert. Under

~~_____~~ So, we made that change to this section, as well as to the table of contents, and any reference that would correspond. Also, there are other minor changes as you will see in the tracked changes. **b(4)**

Please contact Dotti Pease (cc'ed above) and please cc me with your response regarding the latest revisions.

Thank you so much, and I will speak with you on Monday if not later today.

Tammie

From: Dupras, Beth [mailto:edupras@bhconsultingservices.com]
Sent: Tuesday, September 18, 2007 1:10 PM
To: Brent-Steele, Tammie
Subject: RE: NDA 22-137: Response to Labeling Deficiencies

Great! Thanks!
Beth

From: Brent-Steele, Tammie [mailto:tammie.brentsteele@fda.hhs.gov]
Sent: Tuesday, September 18, 2007 12:48 PM
To: Dupras, Beth
Cc: Ribbans, Helen
Subject: RE: NDA 22-137: Response to Labeling Deficiencies

Hi Beth,

Thanks very much for the revised labels. We are meeting this afternoon and I will get back to you with any feedback.

Coverage while I'm out:

Dottie Pease
301-796-1434
dorothy.pease@fda.hhs.gov

Back up:

Frank Cross
301-796-0876
frank.crossjr@fda.hhs.gov

They are both my supervisors.

Thanks again,
Tammie

From: Dupras, Beth [<mailto:edupras@bhconsultingservices.com>]
Sent: Tuesday, September 18, 2007 11:12 AM
To: Brent-Steele, Tammie
Cc: Ribbans, Helen
Subject: NDA 22-137: Response to Labeling Deficiencies

Hi Tammie,
As discussed, attached please find a PDF of the submission responding to the Agency's proposed labeling. This submission will be sent to the central document room via FedEx today. Also attached are copies of the documents provided electronically on CD.

We have accepted the proposed changes to the package, and made some additional minor changes. These additional changes are provided as "track changes" in the Annotated Changes version of the package insert.

Please do not hesitate to contact me if you have any questions!
Best regards,
Beth

Elizabeth N. Dupras, RAC
Senior Project Manager
B&H Consulting Services, Inc.
908-704-1691 x223
908-704-1693 (fax)
edupras@bhconsultingservices.com

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9/21/2007

REQUEST FOR SEALD CONSULTATION

TO (Division/Office):

Study Endpoints and Label Development Team (SEALD)
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411

FROM (Division/Office):

Division of Drug Oncology Products
Tammie Brent, Regulatory Project Manager
Bldg 22 RM 2175
301-796-1409

DATE of REQUEST
August 7, 2007

NDA/BLA/IND NO.
22-137

SERIAL NO/SUPPL. NO

TYPE OF DOCUMENT
NDA 505 (b) (2)

DATE OF DOCUMENT
November 22, 2006

NAME OF DRUG
Fludarabine Phosphate for
Injection

MEETING DATES FOR SUBMISSION
Internal: Sponsor:

CLASSIFICATION OF DRUG

REQUESTED COMPLETION DATE
August 28, 2007

NAME OF SPONSOR or INVESTIGATOR (for investigator Initiated INDs): EBEWE Pharma

INDICATION: : 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.

DRUG DEVELOPMENT PHASE & MILESTONE

- pre-IND/pre-BBIND
- PHASE II
- PHASE III
- PRE-NDA/BLA MEETING

- NDA/BLA/sNDA/SBLA REVIEW
- NDA/BLA SAFETY/EFFICACY UPDATE
- RESPONSE TO DEFICIENCY LETTER
- NDA/BLA/sNDA/SBLA RESUBMISSION REVIEW
- ADVISORY COMMITTEE MEETINGS
- LABELING (INITIAL OR REVISION)
- ADVERTISING REVIEW

OTHER (Specify)

STUDY ENDPOINT OR LABELING To BE REVIEWED

STUDY ENDPOINT REVIEW

- TYPE A MEETING PACKAGE
 - CLINICAL HOLD/DISPUTE RESOLUTION
 - SPA RESPONSE
- TYPE B MEETING PACKAGE
 - PRE-IND MEETING
 - END OF PHASE II/Pre-PHASE III
 - PRE-NDA/BLA
- TYPE C MEETING PACKAGE

- SPECIAL PROTOCOL ASSESSMENT REVIEW
- STANDARD PROTOCOL REVIEW
- PROGRESS REPORT
- STATISTICAL ANALYSIS PLAN REVIEW
- ENDPOINT DEVELOPMENT/VALIDATION DOSSIER
- NDA / BLA REVIEW
- AC MEETING

LABELING REVIEW

- PROPOSED LABELING
- FINAL PRINTED LABELING
- LABELING REVISION
- DRUG ADVERTISING
- OTHER (SPECIFY):

CONSULT REVIEW REQUESTED

Please find attached draft (proposed) labeling for NDA 22-137, Fludarabine Phosphate for Injection for your content review. The attached label contains tracked changes proposed by the sponsor as well as the review team. It also contains the comments from the review team to the sponsor. Please also find below a list of questions from the review team regarding this label. These questions were also sent via email to Melissa Furness on August 7, 2007. Please contact Tammie Brent, Project Manager at 301-796-1409 for any questions.

1. The review team feels that the

2. Regarding references, section 15. The team asked do we have to keep all of the references, and if not, what do we have to keep or not keep?

was required to be in the label.

b(4)

b(4)

Appears This Way
On Original

SIGNATURE OF REQUESTER Tammie Brent	METHOD OF DELIVERY (Check one) <input type="checkbox"/> INTEROFFICE MAIL E-MAIL <input type="checkbox"/> HAND -CARRIED <input checked="" type="checkbox"/>
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Appears This Way
On Original

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

/s/

Tammie Brent-Steele
8/7/2007 02:54:23 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-137

INFORMATION REQUEST LETTER

EBEWE Pharma Ges. m.b.H. Nfg. KG c/o B&H Consulting Services Inc.
Attention: Elizabeth Dupras, R.A.C.
Project Manager
55 North Gaston Avenue
Sommerville, NJ 08876
US

Dear Ms. Dupras,

Please refer to your November 24, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fludarabine phosphate injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1.

2.

3.

b(4)

If you have any questions, call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

(See appended electronic signature page.)

Ravi Harapanhalli, PhD
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Ravi Harapanhalli
6/14/2007 03:20:25 PM

Brent-Steele, Tammie

To: bkunst@bhconsultingservices.com; Dupras, Beth
subject: CMC comments Re: NDA 22-137 Fludarabine

Attachments: Fax CMC comments 3-22-07.doc

Hello Bridget,

Please find attached a fax document that contains comments from our CMC reviewer regarding your NDA 22-137 submission for Fludarabine Phosphate. The reviewer requests that responses to comments be submitted in order of ease of response, as opposed to waiting until you have a full response to each comment.

Please let me know if you have any questions at all.

Have a great afternoon!

Thanks,
Tammie



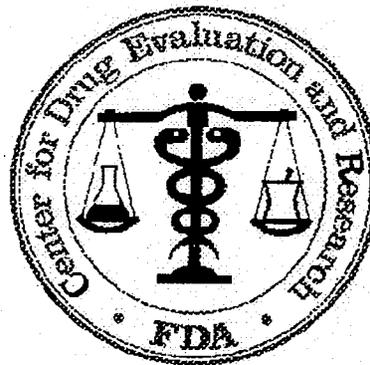
Fax CMC comments
3-22-07.doc (...)

Tammie Brent RN MSN
Regulatory Project Manager
FDA/CDER/OND/OODP
10903 New Hampshire Ave.
Bldg 22 Rm 2175
Silver Spring MD 20993
h: 301-796-1409
Fax 301-796-9845
Email tammie.brentsteele@fda.hhs.gov

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266



To: Elizabeth Dupras, RAC

From: Tammie Brent RN MSN

Fax: 908-704-1693

Fax: (301) 796-9845

Phone: 908-704-1691 ext. 223

Phone: (301) 796-1409

Pages, including cover sheet: 2

Date: March 22, 2007

Re: CMC comments Re: NDA 22-137 Fludarabine Phosphate Injection

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Comments: Please refer to your November 22, 2006 NDA 22-137 submission for Fludarabine Phosphate Injection. We have the following comments from our CMC reviewer:

Pursuant to your New Drug Application NDA 22-137 [Fludarabine Phosphate Injection], please provide the following information regarding the container-closure system:

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.

b(4)

The reviewer kindly request that you submit responses to comments in order of ease of response, rather than waiting until a complete response can be drafted.

Please do not hesitate to contact me if you have any questions or concerns.

Thank you very much,

**Tammie Brent, RN, MSN
Regulatory Project Manager**

**Appears This Way
On Original**

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-137 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Fludarabine Phosphate Injection
Established Name:
Strengths: 50mg/2ml

Applicant: EBEWE Pharma
Agent for Applicant (if applicable): Elizabeth Dupras, RAC B&H Consulting Services, Inc.

Date of Application: November 22, 2006
Date of Receipt: November 24, 2006
Date clock started after UN:
Date of Filing Meeting: January 5, 2007
Filing Date: January 23, 2007
Action Goal Date (optional):

User Fee Goal Date: September 24, 2007

Indication(s) requested: Treatment of 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.

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format? All Labeling is submitted in electronic, SPL, PLR format

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 73,601

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 5, 2007

NDA #: 22-137

DRUG NAMES: Fludarabine Phosphate Injection

APPLICANT: EBEWE Pharma

BACKGROUND: Per Sponsor: Fludarabine Phosphate Injection is indicated for the treatment of 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. This indication is the same indication listed for drug product, Fludara (fludarabine phosphate) for injection, marketed by Berlex Laboratories (NDA 20-038; approved 18 April 1991).

ATTENDEES: R. Justice, A. Ibrahim (Via phone), V. Kwitkowski, S. Pope

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Reviewer

Medical:	Virginia Kwitkowski
Pharmacology:	Doo Lee Ham
Chemistry:	Sarah Pope, Mark Sassaman
Clinical Pharmacology:	Gene Williams
Microbiology, sterility:	Bryan Riley
DSI:	
OPS:	
Regulatory Project Management:	Tammie Brent
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
STATISTICS	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
CLINICAL PHARMACOLOGY			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
• Clin. Pharm. study site audits(s) needed?					YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
PHARMACOLOGY/TOX	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
• GLP audit needed?					YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
CHEMISTRY			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
• Establishment(s) ready for inspection?					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
• Sterile product?					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
If yes, was microbiology consulted for validation of sterilization?					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments: Label Only

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
- Convey document filing issues/no filing issues to applicant by Day 74.

Tammie Brent
Regulatory Project Manager
Version 6/14/2006

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Fludara 20-038

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s): Fludara

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application changes how supplied from a lyophilized formulation to a formulation already in solution. The sponsor has removed Mannitol, an ingredient in the referenced listed drug, Fludara, from its formulation, and added Disodium hydrogenphosphate dihydrate, a buffering agent, to its formulation.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? YES NO

(See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)).

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the

Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) Fludara. and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Non-Clinical and Clinical sections rely on the studies cited in the Fludara Label.

Chemistry relies on information provided by the sponsor.

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Tammie Brent-Steele
2/2/2007 05:17:57 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-137

EBEWE Pharma Ges.m.bH Nfg.KG
Attention: Elizabeth N. Dupras, RAC
Project Manager
US Agent for EBEWE Pharma
B&H Consulting Services, Inc.
55 North Gaston Avenue
Somerville, New Jersey 08876

Dear Ms. Dupras:

Please refer to your November 22, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fludarabine Phosphate Injection, 25mg/ml.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on January 23, 2007, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

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

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Tammie Brent, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

{See appended electronic signature page}

Tammie Brent, RN, MSN
Regulatory Project Manager

**Appears This Way
On Original**

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/s/

Tammie Brent-Steele
1/26/2007 09:47:33 AM
Letter Revision 1-26-07

REQUEST FOR CONSULTATION

TO (Office/Division): Office of Microbiology
Attention: Jim McVey, Ph.D., David Hussong, Ph.D.

FROM (Name, Office/Division, and Phone Number of Requestor):
Karl Stiller, ONDQA
x6-1993

DATE January 17, 2007	IND NO.	NDA NO. 22-137	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT November 24, 2006
NAME OF DRUG Fludarabine phosphate injection		PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE June 1, 2006

NAME OF FIRM: Ebewe Pharma

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|---|

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|---|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the microbiology data of the application. Volumes have been ordered through the clinical project manager, and will be delivered to the microbiology reviewer.

SIGNATURE OF REQUESTOR:
Karl Stiller

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Karl Stiller

1/17/2007 10:27:18 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-137

NDA ACKNOWLEDGMENT

EBEWE Pharma GEs.m.bH Nfg.KG
Attention: Elizabeth N. Dupras, RAC
Project Manager
US Agent for EBEWE Pharma
B&H Consulting Services, Inc.
55 North Gaston Avenue
Somerville, New Jersey 08876

Dear Ms. Dupras:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Fludarabine Phosphate Injection, 25mg/ml

Review Priority Classification: Standard (S)

Date of Application: November 22, 2006

Date of Receipt: November 24, 2006

Our Reference Number: NDA 22-137

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 January 23, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 24, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

NDA 22-137

Page 2

Please cite the NDA 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 Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Tammie Brent, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

{See appended electronic signature page}

Tammie Brent, RN, MSN
Regulatory Project Manager
Division of Drug Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Tammie Brent-Steele
1/16/2007 03:05:27 PM

Brent-Steele, Tammie

From: Dupras, Beth [edupras@bhconsultingservices.com]
Sent: Tuesday, January 16, 2007 9:12 AM
To: Brent-Steele, Tammie
Cc: Ribbans, Helen
Subject: RE: Sponsor presentation date

Hi Tammie,
For your information, the participants that will attend our meeting Friday are as follows:

- Dr. Wolfgang Schmitzberger; Chief Operation Officer, EBEWE
- Dr. Heinz Schnait; Head of Pharmaceutical Development, EBEWE
- Joel Rosenstack; Vice President, Operations, Parenta Pharmaceuticals an EBEWE Pharma Company
- Elizabeth N. Dupras, RAC; Senior Project Manager; B&H Consulting Services, Inc. (US Agent for EBEWE)

Best regards,
Beth

From: Dupras, Beth
Sent: Tuesday, January 16, 2007 8:13 AM
To: 'Brent-Steele, Tammie'
Cc: Ribbans, Helen
Subject: RE: Sponsor presentation date

Hi Tammie,
As requested, attached are two presentations that EBEWE will speak from at our meeting on Friday afternoon.

We thank you for your time and look forward to a productive meeting. If you should require further information, please contact me at 908-704-1691, ext. 223.

Best regards,
Beth

From: Brent-Steele, Tammie [mailto:tammie.brentsteele@fda.hhs.gov]
Sent: Thursday, December 21, 2006 2:36 PM
To: Dupras, Beth
Subject: Sponsor presentation date

Hi Beth,

Please find attached a copy of the fax document containing the date for your sponsor presentation on January 19, 2007. Please let me know if you have any questions at all. I will also fax this document to you today.

Thank you!

1/19/2007

Tammie

<<Fax Sponsor Presentation Date.doc>>

**Appears This Way
On Original**

Financial Disclosure

Brent-Steele, Tammie

From: Cross Jr, Frank H
Sent: Tuesday, January 09, 2007 1:11 PM
To: Ripper, Leah W
Cc: Brent-Steele, Tammie
Subject: RE: Financial Disclosure Forms - 505b2 Application

Thanks. That's what I thought too.

Frank

-----Original Message-----

From: Ripper, Leah W
Sent: Tuesday, January 09, 2007 1:02 PM
To: Cross Jr, Frank H
Subject: Re: Financial Disclosure Forms - 505b2 Application

No, they have to use and sign our forms.

----- Original Message -----

From: Cross Jr, Frank H
To: Ripper, Leah W
Sent: Tue Jan 09 11:22:44 2007
Subject: Financial Disclosure Forms - 505b2 Application

Hi Leah,

Is a signed statement sufficient for financial disclosure is there are no investigators to declare or are we required to have a "3454."?

Please advise.

Thanks,
Frank

Patent Information

Brent-Steele, Tammie

From: Cross Jr, Frank H
Sent: Tuesday, January 09, 2007 1:09 PM
To: Holovac, Mary Ann
Cc: Brent-Steele, Tammie
Subject: RE: Patent Form Question

Thanks, Mary Ann

Frank

From: Holovac, Mary Ann
Sent: Tuesday, January 09, 2007 1:01 PM
To: Cross Jr, Frank H
Subject: RE: Patent Form Question

There is a box to check off stating no patents. We don't need the 3542a (pre approval) form at all but should have the 3542 completed with the no pats box checked off post approval. Thanks.

From: Cross Jr, Frank H
Sent: Tuesday, January 09, 2007 12:02 PM
To: Holovac, Mary Ann
Subject: RE: Patent Form Question

Does the orange book staff need the form filled out by the applicant if there are no patents to declare?

Thanks,

Frank

From: Holovac, Mary Ann
Sent: Tuesday, January 09, 2007 11:38 AM
To: Cross Jr, Frank H
Subject: RE: Patent Form Question

Hi Frank,

No, they just need to have an authorized official sign...and that can be the NDA holder, patent holder or their reps...and indicate all that apply in the signoff boxes. Only the NDA holder can submit to the agency...ie if the patent holder is a different entity, they can't directly submit but may sign the form for the NDA holder to then submit.

Don't need multiple signatures. Submission of patent information is required. Info submitted only on 3542 (not 3542a) is used for Orange Book publication post approval.

Thanks.

Mary Ann

From: Cross Jr, Frank H
Sent: Tuesday, January 09, 2007 11:32 AM

To: Holovac, Mary Ann
Subject: RE: Patent Form Question

Is an applicant required to have both the signature of the US rep and the Foreign rep?

Thanks,

Frank

From: Cross Jr, Frank H
Sent: Tuesday, January 09, 2007 11:31 AM
To: Holovac, Mary Ann
Subject: Patent Form Question

Hi Mary Ann,

The Applicant has only submitted a signed statement that a patent search was done.

Are they required to submit the 3542a?

Please advise.

Thanks,

Frank

Brent-Steele, Tammie DMETS

From: Cross Jr, Frank H
Sent: Tuesday, January 09, 2007 12:49 PM
To: Smith, Diane
Cc: Chan, Samuel; Birdsong, Sandra; Brent-Steele, Tammie
Subject: RE: Tradename Consult for NDA 22-137

Thanks,

Frank

From: Smith, Diane
Sent: Tuesday, January 09, 2007 12:44 PM
To: Cross Jr, Frank H
Cc: Chan, Samuel; Birdsong, Sandra
Subject: RE: Tradename Consult for NDA 22-137

Yes please send it to DMETS for review.

Sam Chan is now the OSE PM for Oncology.

From: Cross Jr, Frank H
Sent: Tuesday, January 09, 2007 11:28 AM
To: Smith, Diane
Subject: Tradename Consult for NDA 22-137

Hi Diane,

We have a 505b2 NDA in house. No Tradename is proposed by the applicant - they will be using the established name, fludarabine phosphate injection, 25 mg/mL

Does DMETS want a consult? Please advise.

Thanks,

Frank

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 22-137 SUPP TYPE & # 0-000 Division 150 UFID # 3006894
 Applicant Name: EBEWE PHARMA Drug Name: Fludarabine Phosphate Inj.

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?
 Yes No
2. Firm in Arrears?
 Yes No
3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees"
<http://www.fda.gov/cder/guidance>
 Yes No (explain in comments)
4. Administrative Split? (list all NDA#s and Divisions)

NDA #/Doc Type	Div.	Fee? (Y/N)
5. Type 6?
 Yes No
 Type 6 to which other application?
 NDA # _____ Supp Type & # _____
6. Clinical Data Required for Approval? (Check one)
 Yes*
 Yes, by reference to another application.
 NDA # _____ Supp Type & # _____
 No

* Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)"
<http://www.fda.gov/cder/guidance>
 Yes No To be determined
8. Subpart H (Accelerated Approval/Restricted Distribution)?
 Yes No To be determined
9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)
List of exclusions:
 2 - No fee - administrative split
 4 - No fee - 505b2
 7 - Supplement fee - administrative split
 9 - No fee Subpart H supplement - confirmatory study
 11 - No fee Orphan Exception
 13 - No fee State/Federal exemption from fees
10. Waiver Granted?
 Yes (letter enclosed) No
 Select Waiver Type below: Letter Date: _____
 Small Business Barrier-to-Innovation
 Public Health Other (explain)
11. If required, was the appropriate fee paid?
 Yes No
12. Application Review Priority
 Priority Standard To be determined
13. Fast Track/Rolling Review Presubmission?
 Yes No

Comments

James D. [Signature] 12-19-06
 PM Signature/Date To Doc Rm.

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

CC: original archival file
 HFD-007

Processor Name & Date

QC Name & Date

22 November 2006

RECEIVED

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Drug Oncology Products, HFD-150
5901-B Ammendale Road
Beltsville, MD 20705-1266

NOV 28 2006

CDER White Oak DR 1

CDER/CDR

NOV 24 2006

RECEIVED

**RE: 505(b)(2) New Drug Application
Fludarabine Phosphate Injection**

Dear Sir or Madam: N22-137

Pursuant to 21 CFR 314.50, on behalf of EBEWE Pharma Ges.m.b.H. Nfg.KG (EBEWE), we are submitting a New Drug Application (NDA) for Fludarabine Phosphate Injection.

Fludarabine Phosphate Injection is indicated for the treatment of 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. This indication is the same indication listed for drug product, Fludara® (fludarabine phosphate) for Injection, marketed by Berlex Laboratories (NDA 20-038; approved 18 April 1991).

Fludarabine phosphate drug substance is manufactured _____
The manufacture of fludarabine phosphate is considered confidential information to EBEWE. Letters authorizing FDA to reference _____ Type II Drug Master File (DMF) _____ are included in Module 1.

b(4)

The application consists of 7 volumes in Common Technical Document (CTD) format, including sterility assurance data. This submission contains three complete copies of the application: one archival copy, one review copy and one field copy; as well as two additional copies of the Methods Validation Package (Module 3.2.R.3.P). A CD containing electronic copies of the proposed labeling is also included in the archival copy. B&H Consulting Services, Inc. certifies that we have taken precautions to ensure that the electronic labeling is free of computer viruses, and authorizes the Agency to use antivirus software, as appropriate.

Reference is made to the Type B, Pre-NDA Meeting requested by EBEWE to discuss the submission for Fludarabine Phosphate Injection, and the subsequent Agency responses received 01 February 2006. These responses are included in Module 1, and summarize the Agency's agreement to the submission strategy.

The proposed package insert labeling for Fludarabine Phosphate Injection is provided in Full Prescribing Information (FPI) format. The labeling text is the same as the reference product, Fludara® (fludarabine phosphate) for Injection, with the exception of the product name, and the changes specified in the Annotated Draft Package Insert in FPI Format that reflect the formulation differences in EBEWE's proposed drug product.

The CD containing electronic labeling includes the Structured Product Labeling (SPL) of the draft package insert. EBEWE has drafted the highlights section based on the information in the Fludara® (fludarabine phosphate) for Injection labeling. Since EBEWE does not have right of reference to the Fludara® (fludarabine phosphate) for Injection clinical studies that are the basis of this labeling, the sponsor requests Agency agreement for the highlights section prior to completing the SPL formatting for this section.

A copy of the letter designating B&H Consulting Services, Inc. to act as US Agent on behalf of EBEWE is appended to this letter.

If you should require further information, please contact me at 908-704-1691, ext. 223.

Sincerely,



Elizabeth N. Dupras, RAC

Project Manager

B&H Consulting Services, Inc.

US Agent for EBEWE Pharma Ges.m.b.H. Nfg.KG

edupras@bhconsultingservices.com

The full name and address of the applicant are:

EBEWE Pharma Ges.m.b.H. Nfg.KG

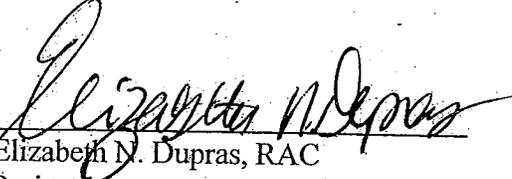
Mondseestraße 11

4866 Unterach

AUSTRIA

Field Copy Certification

B&H Consulting Services, Inc. certifies that the field copy of this NDA is a true copy of the information contained in the archival and review copies of the NDA for Fludarabine Phosphate Injection submitted on behalf of EBEWE Pharma Ges.m.b.H. Nfg.KG.


Elizabeth N. Dupras, RAC
Project Manager
B&H Consulting Services, Inc.
US Agent for EBEWE Pharma Ges.m.b.H. Nfg.KG

20Nov06
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT EBEWE Pharma Ges.m.b.H. Nfg.KG		DATE OF SUBMISSION 11/22/06
TELEPHONE NO. (Include Area Code) +43-7665-8123-0		FACSIMILE (FAX) Number (Include Area Code) +43-7665-8123-129
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Mondseestraße 11 4866 Unterach AUSTRIA		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE B&H Consulting Services, Inc. 55 North Gaston Avenue Somerville, NJ 08876 (p) 908-704-1691 (f) 908-704-1693

CDER/CDR
NOV 24 2006

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Fludarabine Phosphate Injection		PROPRIETARY NAME (trade name) IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)		CODE NAME (If any)
DOSAGE FORM: Injectable	STRENGTHS: 25 mg/mL	ROUTE OF ADMINISTRATION: Injection

RECEIVED

(PROPOSED) INDICATION(S) FOR USE:
Fludarabine phosphate is a _____ substance. It is indicated in human medicine for the treatment of 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.

b(4)

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Fludara® (fludarabine phosphate) for

Name of Drug Injection Holder of Approved Application Berlex Laboratories

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Initial NDA

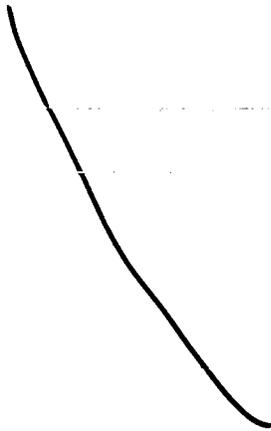
PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 7 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug Substance:



b(4)

Drug Product Manufacture:

All the manufacturing steps of the final dosage form (including final packaging, release testing and stability testing) are performed by:

EBEWE Pharma Ges.m.b.H. Nfg.KG
Mondseestraße 11
4866 Unterach
AUSTRIA

FEI No.: 3002829723

Dr. G. Berliz
Head of Quality Management

Phone: +43-7665-8123-0
Fax: +43-7665-8123-129
Email: Guenther.Berliz@ebewe.com

Currently available for inspection.

The tests for bacterial endotoxins and sterility will be conducted by:



b(4)

Currently available for inspection.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)



b(4)

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Request for Waiver from Conducting Pediatric Studies
Request for Waiver from Providing Evidence of In Vivo Bioequivalence

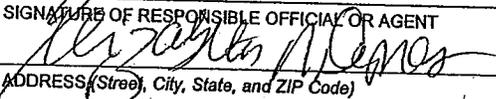
CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Elizabeth N. Dupras, RAC; Project Manager	DATE: 11/22/06
ADDRESS (Street, City, State, and ZIP Code) 55 North Gaston Avenue; Somerville, NJ 08876		Telephone Number (908) 704-1691 ext. 223

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE
COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>EBEWE PHARMA GES M B H NFG KG Guenther Berliz Elizabeth Dupras B&H Consulting Services, Inc. 55 N. Gaston Avenue Somerville NJ 08876 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>N 22-137</p>
<p>2. TELEPHONE NUMBER</p> <p>908-704-1691 223</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>Fludarabine Phosphate Injection (Fludarabine Phosphate Injection)</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006894</p>
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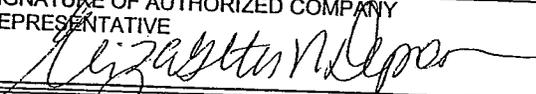
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input checked="" type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> 	<p>TITLE</p> <p>PROJECT MANAGER</p>	<p>DATE</p> <p>22 Nov 2006</p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$.00

Form FDA 3397 (12/03)

Close Print Cover sheet



Request for Waiver from Providing Evidence of In Vivo Bioequivalence

Pursuant to 21 CFR 320.22(b)(1) and (e), EBEWE Pharma Ges.m.b.H. Nfg.KG (EBEWE) is requesting a waiver from providing evidence of *in vivo* bioequivalence of Fludarabine Phosphate Injection relative to the reference listed drug, Fludara® (fludarabine phosphate) for Injection.

While the formulations differ in excipients, in EBEWE's scientific and medical opinion, the differences will not impact the bioequivalence of the formulation. _____ is used in the formulation of the reference listed drug, but not the EBEWE formulation. In lyophilized formulations, _____ cake structure with good mechanical properties.

b(4)

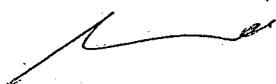
Disodium hydrogenphosphate dihydrate is added to the EBEWE formulation as a _____. The additional excipient is commonly used in pharmaceutical formulations. Disodium _____ phosphate dihydrate is also included in the FDA's Inactive Ingredients Database, and is listed as safe for use in injections and infusions.

b(4)

As agreed in the Agency's response to the pre-NDA meeting briefing package questions, no further nonclinical or clinical studies are required. EBEWE has identified and characterized the differences in the excipients and provided information to show that the differences do not affect the safety or efficacy of the proposed drug.

Finally, pursuant to 21 CFR 320.22(e), FDA may waive the requirement for the submission of *in vivo* bioequivalence data if the waiver is compatible with the protection of the public health.

EBEWE firmly believes that a waiver of *in vivo* bioequivalence requirements is scientifically warranted and compatible with the protection of the public health.



Dr. M. Mussill
Head of Regulatory Affairs
EBEWE Pharma Ges.m.b.H. Nfg.KG

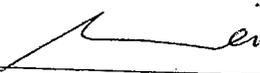
17 November 2006
Date

EBEWE Pharma



Translation Certification

The German documentation provided in this application has been translated to English by EBEWE Pharma Ges.m.b.H. Nfg.KG. The English translations are provided followed by the German versions. EBEWE Pharma Ges.m.b.H. Nfg.KG certifies that the translations are accurate representations of the original German versions.



Dr. M. Mussill
Head of Regulatory Affairs
EBEWE Pharma Ges.m.b.H. Nfg.KG

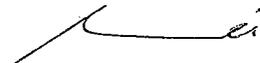
15 Nov 2006
Date

EBEWE Pharma



Request for Categorical Exclusion from an Environmental Assessment

EBEWE Pharma Ges.m.b.H. Nfg.KG certifies that the requested action, approval of the NDA for Fludarabine Phosphate Injection, meets the criteria for categorical exclusion defined in 21 CFR 25.31(a), and that to the knowledge of EBEWE Pharma Ges.m.b.H. Nfg.KG, no extraordinary circumstances exist as defined in 21 CFR 25.21. Thus, no environmental assessment is required according to 21 CFR 25.20(1).



Dr. M. Mussill
Head of Regulatory Affairs
EBEWE Pharma Ges.m.b.H. Nfg.KG

15 Nov 2006
Date