CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208264Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109219

MEETING MINUTES

Adienne Pharma & Biotech
Attention: R.J. Tesi, M.D.
Chief Medical Officer
P.O. Box 9000 PMB 168
Edgartown, MA 02539

Dear Dr. Tesi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tepadina® (thiotepa).

We also refer to the meeting between representatives of your firm and the FDA on April 20, 2011. The purpose of the meeting was to obtain the Division's concurrence that the proposed content will support the filing and approval of an NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tyree Newman, Regulatory Project Manager at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Deputy Division Director (Acting)
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 20, 2011 / 3:00 – 4:00 PM
Meeting Location:	White Oak, Building 22, Room 1311
Application Number:	IND 109219
Product Name:	Tepadina® (thiotepa)
Indication:	For the treatment prior to hematopoietic progenitor cell transplantation for lymphoma
Sponsor/Applicant Name:	Adienne Pharma & Biotech
Meeting Chair:	Edvardas Kaminskas, M.D.
Meeting Recorder:	Tyree Newman, B.S.

FDA ATTENDEES
Edvardas Kaminskas, M.D., Deputy Director (Acting)
Albert Deisseroth, M.D., Ph.D., Medical Officer
Donna Przepiorka, M.D., Ph.D., Medical Officer – *Via phone*
Marcus Cato, M.B.A., Regulatory Health Project Manager
Haleh Saber, Ph.D., Pharmacology/Toxicology Supervisor
Alexander Putman, Ph.D., Pharmacologist
Robert Kane, M.D., Deputy Director Safety (Acting) – *Via phone*
Diane Leaman, B.S., Safety Regulatory Project Manager – *Via phone*
Julie Bullock, Ph.D., Clinical Pharmacology Team Leader
Young Jin Moon, Ph.D., Clinical Pharmacology Reviewer
Mark D. Rothmann, Ph.D., Biostatistics Team Leader
Kallappa Koti, Ph.D., Biostatistics Reviewer
Sarah Pope Miksinski, Ph.D., Branch Chief, ONDQA/DPAMS/Branch 5
Constance Robinson, R.A.C., P.M.P., Regulatory Information Specialist
Francis Godwin, M.B.A., Compliance Officer
Tyree Newman, B.S., Regulatory Health Project Manager

SPONSOR ATTENDEES
Antonio Francesco Di Naro, Chem. Pharm.D., Ph.D., President and CEO of Adienne
RJ Tesi, M.D., Chief Medical Officer and Director of Clinical Development, Adienne
(b) (4)
Joe O'Neill, General Consulting


(b) (4)

1.0 BACKGROUND

Adienne Pharma & Biotech requested a Type B meeting on February 4, 2011, to discuss the adequacy of their data to support the filing and approval of Tepadina (thiotepa) as a conditioning treatment prior to hematopoietic progenitor cell transplantation for lymphoma. Adienne also desired to obtain the Division's concurrence that the proposed content would support the filing and approval of an NDA. On February 11, 2011, the Division sent Adienne Pharma & Biotech the meeting request granted letter.

On April 13, 2011, the Division emailed Adienne Pharma & Biotech preliminary responses to their questions contained in the meeting information package dated March 21, 2011.

2. DISCUSSION

2.1. Clinical

QUESTION 1-

a. In previous communication (FDA draft responses - September 21, 2010), the FDA recommended that ADIENNE narrow its label to a therapeutic indication that can be supported by validated clinical data. ADIENNE agrees with this recommendation and has narrowed the request for labeling (b) (4) *ADIENNE will pursue a pediatric indication* (b) (4) ***Does the FDA agree with this strategy?***

FDA Response: **No.** (b) (4) (b) (4)

Discussion: **The Sponsor and the Division discussed the appropriate pathways that should be taken to move forward. There was agreement that the Sponsor would attempt to identify a pivotal trial design that would fulfill the requirements of the 505(b)(2) pathway. The Agency expressed its interest and willingness in working with the Sponsor to find an appropriate trial design.**

b. (b) (4)

[redacted] ***Does the FDA agree*** [redacted]

FDA Response: **No.** [redacted]

Discussion: **See discussion under Question 1a.**

c. [redacted] ***Does the FDA agree with these primary efficacy end-points?***

FDA Response: **No.** [redacted]

Discussion: **See discussion under Question 1a.**

d. [redacted] ***Does the FDA agree with this approach?***

FDA Response: **No. (See responses to Questions above.)**

Discussion: **See discussion under Question 1a.**

e. [redacted] ***Does the FDA agree with this approach?***

FDA Response: **No.** [redacted]

Discussion: **See discussion under Question 1a.**

2.2. Clinical Pharmacology

QUESTION 2

a. TEPADINA® is thiotepa with no excipients [redacted] *given by injection after reconstitution with sterile water and dilution into an appropriate intravenous solution for administration. ADIENNE believes the published studies of pharmacology and pharmacokinetics accurately reflect the pharmacology and pharmacokinetics of TEPADINA®.* ***Does the FDA agree?***

FDA Response: The adequacy of the published studies of pharmacology and pharmacokinetics to support labeling of TEPADINA® will be a review issue.

Discussion: No discussion occurred.

b. The pharmacology of thiotepa has been extensively studied. ADIENNE plans to refer to published studies of the use high-dose thiotepa for conditioning prior stem cell transplant to support the clinical pharmacology of TEPADINA®. ADIENNE does not plan new pharmacology, pharmacodynamic or pharmacokinetic studies. ***Does the FDA agree that no additional pharmacology, pharmacodynamic or pharmacokinetic studies are needed for NDA approval?***

FDA Response: We remind you of previous clinical pharmacology comments for the pre-IND meeting package:

(b) (4)

These data should be acquired and submitted as part of the NDA.

Discussion: No discussion occurred.

2.3. Manufacturing

(b) (4)

API presented in the CMC section in the application has, in both cases, been manufactured by [redacted] *in compliance with requirements of United States Pharmacopeia (USP)* [redacted] *holds a current US DMF for thiotepa, approved on March 20, 2009.* [redacted] *supplies thiotepa USP* [redacted] *for the manufacture of thiotepa for injection and is registered as a Drug Establishment with the FDA (Registration no:* [redacted]*; Labeller Code Number* [redacted]*).*
Does the FDA agree that the safety and efficacy will accurately reflects the safety and efficacy of the proposed product?

FDA Response: **Your approach is reasonable provided that the quality of the drug substance is identical (i.e., there has not been any significant manufacturing changes that have caused a significant change in the quality of the drug substance). If there are any significant changes or variations in the respective drug substance quality, or if you are unable to adequately substantiate the comparative quality of the drug substance, your approach will not be acceptable.**

Discussion: **No comments from Sponsor.**

2.4. Quality

QUESTION 4

a. Eighteen-month stability data are currently available for three TEPADINA® 100 mg pre-validation batches and show a [redacted]*%. Stability studies were performed in accordance with the Note for Guidance, Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02, rev 1) on three pre-validation batches of TEPADINA® 100 mg. For the 100 mg strength presentation, 24 months data will be available by the time of NDA filing. All test batches are full scale, commercial production batches. The batches are of the same formulation and dosage form in the container closure system proposed for marketing. There are some slight differences in the proposed manufacturing process versus the process that was used to make the pre-validation/stability batches. The proposed changes ensure the validity of the commercial manufacturing process. They have no effect on the stability of the final product. The changes and the risk assessment will be presented in the NDA.* ***Does the FDA agreement with this strategy?***

FDA Response: **Your strategy may be acceptable if your stability package submitted in the NDA complies with the recommendations outlined in ICHQ1A(R2) Stability Testing of New Drug Substances and Products. Note that batches used in your stability study should be manufactured by the same synthetic route as, and using a method of manufacture and procedure that simulates the process used to produce the commercial batches. A final determination of acceptability will be made at the time of the NDA review.**

Discussion: **No comments from Sponsor.**

b. ADIENNE has contracted with [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4). *Does the FDA agree with this proposal?*

FDA Response: **Stability data for the 15 mg strength should cover a minimum of 12 months in duration on at least three primary batches and continued for a period of time sufficient to cover the proposed shelf-life. Additional data from accelerated and intermediate storage (if appropriate) conditions can be used to evaluate the effect of temperature excursions outside the label storage conditions.**

Alternatively, you may submit a prior approval supplemental application for the 15 mg strength after approval of your NDA for the 100 mg strength.

Discussion: **No comments from Sponsor.**

c. Would the Agency accept, at the time of submission of the NDA two validation batches for TEPADINA® 100 mg, instead of 3, provided the other validation batch is manufactured, analyzed and approved prior to distribution? We respectfully request consideration because of the following circumstances:

- *TEPADINA® is an orphan drug;*
- *ADIENNE is a mid-size company and the cost of one validation batch is very expensive;*
- *TEPADINA® based on current data, has a short shelf-life of 18 months;*
- *Estimated use of TEPADINA® for the indication will* [redacted] (b) (4) [redacted] (b) (4) *;*
- *The Finished Product Manufacturer has extensive experience* [redacted] (b) (4) [redacted] (b) (4) *ADIENNE would like to use the pre-validation batches as stability batches for registration purposes.* ***Does the FDA agree with this proposal?***

FDA Response: **It is the company's responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. The number of lots included in a study is not a performance criteria.**

Concurrent release may be considered for drug products with orphan drug status. Orphan drug status is recognized as a situation where, potentially, distribution of any given batch before completion of the initial process validation study may be justified for the greater public health benefit. With concurrent release, each process qualification batch is essentially released on its own merits without the assurance of quality conferred upon product made by a process proven to be consistent and reproducible, stable, and capable.

For further information regarding FDA's current thinking on Concurrent Release, Orphan drugs, and Process Validation, please see FDA's "Guidance for Industry, Process Validation: General Principles and Practices" Revision 1, January 2011. The guidance can be found at the following link:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Discussion: No comments from Sponsor.

2.5. Regulatory Filing Strategy

QUESTION 5

Provided the responses to our questions and the comments we receive from the FDA allow us to move forward with filing the NDA, we expect to file the dossier in the electronic CTD format by the end of June 2011. ADIENNE may request a separate meeting on the electronic filing in the near future. ***Does the FDA agree with this strategy?***

FDA Response: For clarification, do you intend on submitting the application in eCTD format which is CDER's preferred format and standard format for electronic submissions?

Yes, it's acceptable to have a separate meeting regarding the electronic submission. If this is your first eCTD submission, it's recommended that a sample eCTD be completed prior to submitting an actual submission. Please refer to the eCTD Sample Web page or contact ESUB (esub@fda.hhs.gov) for more information.

Discussion: The Sponsor confirmed that the application would be submitted in eCTD format.

3.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Sponsor will forward	Sponsor	N/A

proposed study design(s) to the RPM in order to receive feedback from the FDA		

4.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for this meeting.

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

/s/

TYREE L NEWMAN
04/26/2011

EDVARDAS KAMINSKAS
04/26/2011
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