CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208255Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208255

MEETING MINUTES

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
781 Chestnut Ridge Rd.
PO Box 4310
Morgantown, WV 26505

Dear Mr. Talton:

Please refer to your pre-assigned New Drug Application (NDA) 208255 to be submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tenofovir Disoproxil Fumarate, Lamivudine and Efavirenz Tablets, 300 mg/300 mg/400 mg.

We also refer to the teleconference between representatives of your firm and the FDA on March 26, 2015. The purpose of the meeting was to discuss your NDA filing strategy under the provisions of the President's Emergency Plan for AIDS Relief (PEPFAR).

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

If you have any questions, call me at (301) 796-0669.

Sincerely,

{See appended electronic signature page}

David Araojo, PharmD, MS
Program Coordinator
Division of Antiviral Products
Office of Antimicrobial 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:	March 26, 2015 3:30-4:30 pm (ET)
Meeting Location:	Teleconference
Application Number:	208255
Product Name:	Tenofovir Disoproxil Fumarate, Lamivudine and Efavirenz Tablets, 300 mg/300 mg/400 mg.
Indication:	Treatment of HIV-1 Infection
Sponsor/Applicant Name:	Mylan Pharmaceuticals Inc.
Meeting Chair:	David Araojo, PharmD

FDA ATTENDEES
Jeffrey Murray, MD, MPH, DAVP Deputy Director
Linda Lewis, MD, Medical Team Leader
Adam Sherwat, MD, Medical Team Leader
Angelica Dorantes, PhD, OPQ Acting Biopharmaceutics Branch Chief
Stephen Miller, PhD, OPQ CMC Lead
Peter Capella, PhD, OPQ, DIRP II Director
Mark Powley, PhD, Pharmacology Reviewer
David Araojo, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES
Keith Giunta, Director, Regulatory Affairs
Russ Rackley, Vice President, Global Pharmacokinetics
(b) (4), Regulatory Counsel
Melynda Watkins, Project Director, R&D, Clinton Health Access Initiative
Paul Domanico, Senior Director, R&D, Clinton Health Access Initiative

1.0 BACKGROUND

The primary objectives of the meeting are to reach agreement on a regulatory pathway and bioequivalence plan for Tenofovir Disoproxil Fumarate, Lamivudine and Efavirenz Fixed Dose Combination Tablets, 300 mg/300 mg/400 mg (TLE400) using ENCORE1 (Efficacy of 400 mg Efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naïve adults) as the basis for filing a New Drug Application. A 505(b)(2) NDA will be filed for this combination product,

referencing the innovators. Clinical reference to the ENCORE1 data will be obtained from the data owners, via reference to an IND in which the data will be submitted.

FDA sent Preliminary Comments to Mylan Pharmaceuticals, Inc. on March 19, 2015.

2. DISCUSSION

2.1. Clinical

Question 1:

In ENCORE1, subjects were dosed with Truvada® (tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)) tablets, 300 mg/200 mg, and either 2 Efamat™ (efavirenz), 200 mg tablets and 1 placebo tablet for a 400 mg efavirenz dose or 3 Efamat tablets for a 600 mg efavirenz dose. The study utilized commercial supplies of Truvada (Gilead Sciences, California, USA) and Efamat (Mylan Laboratories, India) from the US and India. Mylan proposes the following bioequivalence study in support of the proposed commercial fixed dose combination:

(b) (4)

FDA Response to Question 1:

(b) (4)

Also, we recommend conducting a pharmacokinetic study to evaluate the effect of food on your proposed FDC. The results of this study can potentially support a more flexible labeling language where the FDC can be administered without regard to food if the effect of food on the FDC produces efavirenz exposures comparable to efavirenz exposures following the administration of 600 mg dose, which is deemed to be safe and effective.

Discussion:

Mylan clarified their proposed bioequivalence study will be conducted as a single study comparing the fixed dose combination to the three Reference Listed Drug products. The FDA agreed to this proposal.

Mylan asked if the recommended pharmacokinetic food effect study was required. The FDA stated they will consult the clinical pharmacology team and provide a response after the meeting.

2.2. Administrative

Question 2:
1. Mylan proposes to file a 505(b)(2) NDA consisting of the following sections:
a. CMC: A reference and letters of access to the relevant DMFs for the APIs in TLE400 will be included. A full CMC drug product section containing all relevant TLE400 data will be submitted.
b. Nonclinical: A reference to the innovator nonclinical data will be included.
c. Clinical: A reference to ENCORE1 data as obtained and granted from the data owners will be included. It is anticipated that the ENCORE1 study data owners will file the data in an IND and provide a letter of access to Mylan for right of reference to the data. The results from the pharmacokinetic bioequivalence study described in Section 8.3 will also be included in the NDA.

Does FDA agree with this filing strategy?

FDA Response to Question 2:
We agree with your proposal.

No meeting Discussion

Question 3:
Based on the FDA Guidance document, "User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR," Mylan proposes to request a waiver of the PDUFA fee for the TLE400 NDA filing.
Does FDA agree that the PDUFA fee can be waived for this filing?

FDA Response to Question 3:
Please refer to the October 2006 FDA Guidance for Industry on Fixed Dose Combinations, Co-Packaged Drug Products and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV. Attachment B of the aforementioned guidance lists your proposed product as a three HIV drug combination supported by current clinical data, and therefore, could be eligible for user fee waiver consideration.

Under section 736(a) of the Act, applications that are user fee eligible will be assessed the appropriate fees at the time of submission. An applicant holder may apply for a waiver or reduction of the fees. Please refer to the February 2007 FDA Guidance for Industry on User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR for more information on how to submit a PEPFAR waiver request. FDA encourages applicant holders to submit their PEPFAR waiver requests at least 45 days in advance of submission of an application so that

the request can be evaluated before the fee is due. Please submit your PEPFAR waiver request to:

1. *For US Mail:*

   Prescription Drug User Fee Staff
   Food and Drug Administration
   10001 New Hampshire Avenue, Room 3179
   Silver Spring, MD 20993-0002

2. *For Courier Delivery:*

   Prescription Drug User Fee Staff
   Food and Drug Administration
   10001 New Hampshire Avenue, Room 3179
   Silver Spring, MD 20903

For more information regarding user fees or how to submit a waiver request, please contact the Office of Management, PDUFA User Fee Staff at (301) 796-7900.

Discussion:
Mylan acknowledged FDA's response and agreed to submit the user fee waiver request at least 45 days prior to the NDA submission.

Question 4:
Subject FDC is not recommended for pediatric populations. Accordingly, Mylan intends to seek a waiver from the provisions of Pediatric Research Equity Act (PREA). The Summary of Product Characteristics as approved by WHO is as follows –
Therapeutic Indications:
Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600mg/300mg/300mg Tablet is a fixed dose combination of tenofovir disoproxil fumarate, lamivudine and efavirenz. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 12 years of age and weighing ≥ 40 kg) with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months.

(b) (4) **Therefore, Mylan intends to seek a waiver from PREA requirements for children** (b) (4) (b) (4) **due to safety considerations in using the adult dosages in pediatric patients.**

Does FDA agree with the proposal to seek a waiver from the provisions of PREA?

FDA Response to Question 4:
If you intend to seek full U.S. approval, you are required to comply with PREA because the overall proposed fixed-dose combination product is considered a new active ingredient.

In addition, please note a waiver of the PREA requirement for the proposed drug product may not be granted because it may not meet any of the following criteria: 1) necessary studies are impossible or highly impracticable, or 2) there is evidence strongly suggesting that the drug would be ineffective and/or unsafe in all pediatric groups, or 3) the drug does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients.

Discussion:
Mylan requested clarification of the timing of the PREA waiver request. FDA stated the PREA waiver request could be addressed at the time of full NDA approval. FDA also offered to discuss justifications for the waiver request.

Additional FDA Comment provided in the Preliminary Response to Questions
You should submit all available clinical pharmacokinetic data from ENCORE1 with your application.

Discussion:
Mylan acknowledged that all ENCORE1 PK data will be submitted by the data owners, the Kirby Institute, and right of reference provided to Mylan. Mylan also acknowledged having access to the PK data, which they will summarize in the NDA.

Mylan stated the Kirby Institute will submit the ENCORE1 data to FDA in the 3rd quarter of 2015, two months prior to Mylan's planned NDA submission in the 4th quarter of 2015.

3.0 POST MEETING COMMENTS

1. Refer to Discussion for Question 1 above: Mylan asked if the recommended pharmacokinetic food effect study was required. The FDA stated they will consult the clinical pharmacology team and provide a response after the meeting.

   FDA Clinical Pharmacology Response- The pharmacokinetic food effect study is highly recommended, however, not required.

2. Please rearrange the drug product name by listing the active ingredients in alphabetical order, e.g. Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.

3. Mylan clarified, via email dated March 30, 2015, that they anticipate submitting the NDA late 1st quarter of 2016 or early 2nd quarter of 2016 (calendar quarters).

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide response to Mylan's question if pharmacokinetic food effect study was required	FDA	See above, Section 3.0

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

/s/

DAVID E ARAOJO
04/15/2015