CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202022Orig1s000

Trade Name: EDURANT 25 mg Tablets

Generic Name: rilpivirine

Sponsor: Tibotec, Inc.

Approval Date: May 20, 2011

Indications: Provides for the use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment naïve adult patients.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202022

NDA APPROVAL

Tibotec, Inc.
Attention: Debora Monshizadegan
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Rd
Rm K21410
Titusville, NJ 08560

Dear Ms. Monshizadegan:

Please refer to your New Drug Application (NDA) dated and received July 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EDURANT™ (rilpivirine) 25 mg Tablets.

We acknowledge receipt of your amendments dated August 25, 2010, September 10, 1010, September 24, 2010, October 4, 2010, October 19, 2010, October 27, 2010, October 28, 2010, November 1, 2010, November 8, 2010, November 19, 2010, December 10, 2010, December 15, 2010, December 17, 2010, December 22, 2010, December 27, 2010, January 10, 2011, January 14, 2011, January 31, 2011, February 23, 2011, February 25, 2011, March 9, 2011, March 17, 2011, March 25, 2011, April 8, 2011, April 21, 2011, May 5, 2011, May 11, 2011, May 13, 2011, and May 18, 2011.

This new drug application provides for the use of EDURANT™ (rilpivirine) Tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on May 18, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202022**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available.

If sending via USPS, please send to:

Robert G. Kosko, Jr., Pharm.D., M.P.H.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6249
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS (e.g., UPS, DHL), please send to:

Robert G. Kosko, Jr., Pharm.D., M.P.H.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6249
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

Your application for EDURANT™ (rilpivirine) Tablets was not referred to an FDA advisory committee because of the following reasons:

A) this drug is not the first in its class

B) the safety profile is similar to that of other drugs approved for this indication

C) the clinical study design is similar to previously approved products in the class

D) the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class

E) the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease

F) outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study for subjects from birth to < 12 years of age until January 2018, and in subjects from 12 to < 18 years of age until January 2014 because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

1768-1 Conduct a pediatric safety and antiviral activity study of rilpivirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks in pediatric subjects from birth to <12 years of age.

Final Protocol Submission:	11/2012
Study Completion:	09/2018
Final Report Submission:	03/2019

1768-2 Conduct a pediatric safety and antiviral activity study of rilpivirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks in pediatric subjects from 12 to <18 years of age.

Final Protocol Submission:	N/A
Study Completion:	08/2014
Final Report Submission:	02/2015

Submit clinical protocols to your IND with a cross-reference letter to this NDA. Submit final reports to this NDA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment(s)**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of increased frequency in overall resistance and cross resistance to the NNRTI class and lamivudine/emtricitabine and a signal of a serious risk of a drug-drug interaction with digoxin.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks of resistance and drug-drug interactions.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1768-3 Submit final reports for Week 96 data analyses (safety, efficacy and resistance evaluation) from the ongoing Phase 3 trials TMC278-C209 and TMC278-C215.

The timetable you submitted on May 13, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	N/A
Trial Completion:	N/A
Final Report Submission:	10/2011

1768-4 Conduct a clinical trial in healthy subjects to evaluate the effect of rilpivirine at steady state on the single dose pharmacokinetics of digoxin. The pharmacokinetics of digoxin when coadministered with rilpivirine (test arm) will be compared to the pharmacokinetics of digoxin by itself (reference arm). The primary digoxin pharmacokinetic parameters that will be evaluated are $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}.

The timetable you submitted on May 13, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	11/2011
Trial Completion:	05/2012
Final Report Submission:	10/2012

Submit the protocols to your IND 67,699 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more

information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Robert G. Kosko. Jr., Pharm.D., M.P.H., Regulatory Project Manager, at (301) 796-3979 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Container Labeling

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

/s/

EDWARD M COX
05/20/2011