

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204790Orig1s000

Trade Name: TIVICAY tablets, 50mg

Generic Name: dolutegravir

Sponsor: ViiV Healthcare

Approval Date: August 12, 2013

Indications: Provides for the use of TIVICAY (dolutegravir) tablets, in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
204790Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	X
Officer/Employee List	X
Office Director Memo	X
Cross Discipline Team Leader Review	X
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	X
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204790Orig1s000

APPROVAL LETTER



NDA 204790

NDA APPROVAL

ViiV Healthcare
c/o GlaxoSmithKline
Attention: Martha Anne Auld, RPh
Senior Director, Infectious Diseases, Regulatory Affairs
Five Moore Drive, P.O. Box 13398, Bldg 5.5218
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) dated December 16, 2012, received December 17, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for TIVICAY (dolutegravir) tablets, 50mg.

We acknowledge receipt of your amendments dated: December 17, 2012, January 16, 2013, January 29, 2013, January 31, 2013, February 13, 2013, February 22, 2013, February 28, 2013, March 14, 2013, March 19, 2013, March 28, 2013, March 29, 2013 (2), April 4, 2013, April 8, 2013, April 12, 2013 (3), April 19, 2013 (3), April 24, 2013, April 25, 2013 (2), May 2, 2013, May 6, 2013, May 7, 2013, May 14, 2013, May 21, 2013, May 31, 2013, June 3, 2013, June 12, 2013, June 27, 2013 (2), July 8, 2013 (2), July 11, 2013, July 26, 2013, July 29, 2013, August 2, 2013, August 06, 2013, August 08, 2013, and August 12, 2013.

This new drug application provides for the use of TIVICAY (dolutegravir) tablets, in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.

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.

Based on the provided stability data, the Agency grants a shelf life of 24 months for dolutegravir tablets, 50 mg, when stored in the approved packaging [30 (b) (4) fill count (b) (4)] at 25°C (77°F); excursions permitted from 15 C to 30 C (59 F to 86 F).

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, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available 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 immediate-container labels that are identical to the immediate-container label submitted on June 12, 2013 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 *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 Container Labels for approved NDA 204790.**” Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for dolutegravir was not referred to an FDA advisory committee because this drug is not the first in its class, the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class, and because outside expertise was not necessary as there were no significant issues identified 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 waiving the pediatric study requirement for ages 0 to less than 4 weeks in HIV-infected patients who are naïve to integrase strand transfer inhibitors (INSTI), and for ages 0 to less than 2 years in HIV-infected patients who are INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance for the following reasons:

- We are waiving the pediatric study requirement for 0 to less than 4 weeks of age in INSTI-naïve and INSTI-experienced patients because with improvement in perinatal transmission prevention strategies there are insufficient numbers of neonatal subjects to be enrolled. Further, even when neonates are identified for enrollment, by the time enrollment is accomplished, dosing is initiated, and drug concentrations have reached steady state, the subjects are likely to be older than 4 weeks of age.
- We are waiving the pediatric study requirement for ages 4 weeks to less than 2 years in INSTI-experienced patients because the necessary pediatric study will be impossible or highly impracticable. Only one INSTI agent, raltegravir, is currently approved for pediatric use in the US and European Union. Raltegravir is not yet available in most developing countries, where the burden of pediatric HIV infection is greatest. Therefore enrollment of patients is expected to be challenging for this particular population and pediatric age group.

We are deferring submission of the pediatric studies for ages 4 weeks to less than 12 years in HIV-infected INSTI-naïve patients, and for ages 2 years to less than 18 years in HIV-infected INSTI experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance. This is because the product is ready for approval for use in adults and INSTI-naïve patients ages 12 years and older, and studies in the remaining pediatric populations are either not initiated or 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.

- 2078 -1 Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected integrase strand transfer inhibitor-naïve, pediatric subjects 4 weeks to less than 12 years of age. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the pharmacokinetic study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

Final Protocol Submission:	(completed)
Trial Completion:	05/31/2018
Final Report Submission:	09/30/2018

2078-2 Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected subjects, ages 2 years to less than 18 years, who are integrase strand transfer inhibitor (INSTI) experienced with certain INSTI associated resistance substitutions or clinically suspected INSTI resistance. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the pharmacokinetic study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

Final Protocol Submission:	06/30/2016
Trial Completion:	06/30/2022
Final Report Submission:	01/31/2023

Submit the protocol to your IND 75,382, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

This product is appropriately labeled for use in HIV-infected INSTI-naïve patients, ages 12 years to 18 years for this indication; therefore, no additional studies are needed in this pediatric population.

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 signal of serious risks of toxicity arising with long-term drug use. The safety concerns with dolutegravir tablets include occurrence of the following events that resulted in discontinuation of subjects from clinical trials: hypersensitivity reactions, hepatic enzyme elevations (predominantly in hepatitis B and C infected patients), and development of renal insufficiency or renal failure. In most cases, alternative etiologies or confounding medications or medical conditions were present; however, a causal relationship or contribution to these events by dolutegravir tablets could not be ruled out. New-onset or worsening hepatic or renal toxicity with longer cumulative exposure is a potential risk.

Additionally, the presence of resistance substitutions either predicting treatment failure or developing in subjects taking a dolutegravir containing regimen have been identified in a limited number of viral isolates and thus represents a known serious risk. Therefore, analyses of isolates from any additional patients not responding to or failing treatment are necessary to help physicians determine appropriate use of dolutegravir tablets with respect to patient selection and thereby decrease the likelihood of the known serious risk of treatment failure of subsequent regimens.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be 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 signals of serious risks and the known serious risk.

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

- 2078-3 Submit the final report for 48 week data analyses which should include, but not be limited to safety analyses of hepatic, renal and hypersensitivity events, and resistance substitutions from trial ING111762 in treatment-experienced, integrase strand transfer inhibitor-naïve subjects.

The timetable you submitted on June 27, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	(completed)
Trial Completion:	(completed)
Final Report Submission:	03/2014

- 2078-4 Submit the final report for 48 week data analyses which should include, but not be limited to safety analyses of hepatic, renal and hypersensitivity events, and resistance substitutions from study ING112574 in treatment-experienced, integrase strand transfer inhibitor-experienced subjects.

The timetable you submitted on June 27, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	(completed)
Trial Completion:	01/2014
Final Report Submission:	03/2014

Submit the protocols to your IND 75,382, 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 2078-5 Submit the final report for 48 week data analyses from the ongoing trial ING116529 (Viking-4) evaluating dolutegravir 50 mg twice daily.

The timetable you submitted on June 27, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	(completed)
Trial Completion:	07/2014
Final Report Submission:	10/2014

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 2078-6 Conduct the requested [REDACTED] ^{(b)(4)} testing for drug substance to target [REDACTED] ^{(b)(4)} degradation, evaluate both drug substance and drug product impurities methods using these conditions, and submit the data as a Changes Being Effected in 0 Days Supplement to be filed within 6 months from the date of NDA action.

The timetable you submitted on May 14, 2013, states, that you will conduct this study according to the following schedule:

Final Report Submission: 03/2014

Submit clinical protocols for this product to your IND 75382. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

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
Office of Prescription Drug Promotion
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 Office of Prescription Drug Promotion (OPDP), 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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

You will be contacted by ERG to schedule the interview following this action on your application; ERG will provide specifics about the interview process at that time. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

Edward M Cox, MD, MPH
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
08/12/2013