

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**201917Orig1s000**

***Trade Name:*** INCIVEK 375 mg, Film-Coated Tablets

***Generic Name:*** telaprevir

***Sponsor:*** Vertex Pharmaceuticals, Incorporated

***Approval Date:*** May 23, 2011

***Indications:*** Provides for the use in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C (CHC) in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated, including prior null responders, partial responders, and relapsers.

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## 201917Orig1s000

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*APPLICATION NUMBER:*

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**APPROVAL LETTER**



NDA 201917

**NDA APPROVAL**

Vertex Pharmaceuticals, Incorporated  
Attention: John Weet, Ph.D.  
Vice President, Regulatory Affairs  
130 Waverly Street  
Cambridge, MA 02139

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) dated November 22, 2010 and received November 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INCIVEK™ (telaprevir), 375 mg, Film-Coated Tablets.

We acknowledge receipt of your amendments dated June 24, 2010, July 14, 2010, September 2, 2010, September 20, 2010, October 8, 2010, October 19, 2010, December 1, 2010, December 2, 2010, December 10, 2010, December 13, 2010, December 15, 2010, December 17, 2010, December 21, 2010, December 23, 2010, January 7, 2011, January 13, 2011, January 14, 2011, January 17, 2011, January 19, 2011, January 21, 2011, January 24, 2011, January 27, 2011, January 28, 2011, February 1, 2011, February 4, 2011, February 8, 2011, February 9, 2011, February 10, 2011, February 11, 2011, February 17, 2011, February 18, 2011, February 22, 2011, February 24, 2011, February 28, 2011, March 4, 2011, March 10, 2011, March 11, 2011, March 15, 2011, March 18, 2011, March 22, 2011, March 23, 2011, March 28, 2011, March 30, 2011, March 31, 2011, April 4, 2011, April 6, 2011, April 13, 2011, April 14, 2011, April 15, 2011, April 20, 2011, April 21, 2011, May 9, 2011, May 10, 2011, May 11, 2011, May 12, 2011, May 13, 2011, May 17, 2011, and May 20, 2011.

This new drug application provides for the use of INCIVEK™ (telaprevir) in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C (CHC) in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated, including prior null responders, partial responders, and relapsers.

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 package insert and Medication Guide). 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 enclosed carton and immediate container labels submitted on May 20, 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 201917.**” 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.

## **MARKET PACKAGE**

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

If sending via USPS, please send to:

Myung-Joo Patricia Hong  
Food and Drug Administration  
Center for Drug Evaluation and  
Research  
White Oak Building 22, Room: 6235  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993

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

Myung-Joo Patricia Hong  
Food and Drug Administration  
Center for Drug Evaluation and  
Research  
White Oak Building 22, Room: 6235  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20903

## **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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to under 3 years because necessary studies are impossible or highly impracticable, very few patients aged 0 to under 3 years with CHC require treatment, and peginterferon alfa and ribavirin cannot be used in children under 3 years of age.

We are deferring submission of your pediatric study for ages 3 to 17 years for this application 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. These required studies are listed below.

1771-1      Conduct a pharmacokinetics trial (or subtrial) of telaprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine appropriate dosing for children that will result in exposures similar to those found to be safe and effective in adults.

Final Protocol Submission:      September, 2011  
Trial Completion:                  June, 2014  
Final Report Submission:        October, 2014

1771-2      Conduct a trial to evaluate safety and treatment response of telaprevir in combination with pegylated interferon and ribavirin as measured by sustained virologic response (SVR) in pediatric subjects 3 through 17 years of age, including previously untreated subjects and those who have failed a prior course of pegylated interferon and ribavirin therapy. This trial should include at least 5 years follow-up of pediatric subjects to characterize long-term safety of telaprevir, including growth assessment and sexual maturation in pediatric subjects, to determine the durability of response, and to characterize telaprevir resistance-associated substitutions.

Final Protocol Submission:                  September, 2011  
Trial Completion:                              September, 2014  
Final Report Submission:                      February, 2015  
Long-Term Final Report Submission:        February, 2019

Submit the clinical protocols to your IND 71,832, with a cross-reference letter to this NDA. Submit all final reports to your NDA For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated “**Required Pediatric Assessments.**”

### **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 a serious risk of the emergence of INCIVEK™ (telaprevir) resistance-associated substitutions following treatment failure, including the impact of specific HCV amino acid substitutions on viral susceptibility to INCIVEK™ (telaprevir).

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.

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

#### **Virology**

1771-3 Conduct a study to assess the impact of the following telaprevir treatment-emergent amino acid substitutions on phenotypic susceptibility of telaprevir in the HCV replicon system.

- I132V (genotype 1a and 1b replicon)
- K244R (genotype 1a and 1b replicon)
- K360R (genotype 1a and 1b replicon)
- R155K ± NS4A\_A36V (genotype 1a)
- NS4A\_E53K (genotype 1a and 1b replicon)

The timetable you submitted on May 17, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	July, 2011
Study Completion:	October, 2011
Final Report Submission:	November, 2011

1771-4 Conduct a study to analyze a representative subset of samples from subjects who experienced virologic failure in the Phase 3 studies, but for whom no clear

resistance-associated substitutions in NS3/4A were detected, for the presence of substitutions in NS3/4A protease cleavage sites.

The timetable you submitted on May 17, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission: June, 2011  
Study Completion: July, 2011  
Final Report Submission: August, 2011

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of decreased INCIVEK™ (telaprevir) exposure in patients on hemodialysis (HD).

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

### **Clinical Pharmacology**

1771-5 Conduct a pharmacokinetic trial in subjects with end-stage renal disease (ESRD) on intermittent hemodialysis (HD) to determine the effect of HD on telaprevir exposure, in order to provide dosing recommendations for chronic hepatitis C patients on HD.

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

Final Protocol Submission: April, 2012  
Trial Completion: July, 2013  
Final Report Submission: December, 2013

Submit the protocol to your IND 71, 832, 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 commitments:

**Clinical**

1771-6            Conduct a trial to evaluate treatment response and safety among treatment-naïve and experienced subjects with cirrhosis compared to subjects without cirrhosis.

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

Final Protocol Submission:    September, 2011  
Trial Completion:                March, 2014  
Final Report Submission:       August, 2014

1771-7            Conduct a trial to evaluate treatment response and safety among Blacks/African Americans compared to non-Blacks/African Americans.

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

Final Protocol Submission:    September, 2011  
Trial Completion:                April, 2014  
Final Report Submission:       September, 2014

1771-8            Conduct a trial (VX11-950-115) to evaluate treatment responses and safety among treatment-naïve and experienced HIV/HCV co-infected subjects.

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

Final Protocol Submission:    January, 2012  
Trial Completion:                June, 2014  
Final Report Submission:       December, 2014

## Pharmacogenomics

1771-9 Conduct a genome-wide association study (GWAS) to identify factor(s) associated with severe rash and severe cutaneous adverse reactions following telaprevir/peginterferon/ribavirin using cases from existing DNA sub-studies and appropriately selected controls.

The timetable you submitted on May 17, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October, 2011
Study Completion:	August, 2012
Final Report Submission:	March, 2013

Submit clinical protocols to your IND 71, 832 for this product. Submit all 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.**”

## **ADDITIONAL REQUEST**

In addition to the PMRs and PMCs listed above, we strongly encourage you to increase awareness of the Ribavirin Pregnancy Registry and encourage reporting of patients who become pregnant while taking ribavirin to the Registry.

## **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

We acknowledge receipt of your submission dated November 22, 2010, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for INCIVEK™ (telaprevir) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

## **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 Myung-Joo Patricia Hong, Regulatory Project Manager, at (301) 796-0807.

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  
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EDWARD M COX  
05/23/2011