CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

0202258Orig1s000

Trade Name: Victrelis

Generic Name: boceprevir

Sponsor: Schering Corporation

Approval Date: 05/13/2011

Indications: For the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients, 18 years of age and older, with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

0202258Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202258

NDA APPROVAL

Schering Corporation
Attention: Thomas J. Chambers, M.D.
Director, Global Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454-1099

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) dated November 10, 2010, received November 15, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VICTRELIS™ (boceprevir) 200 mg capsules.

We acknowledge receipt of your amendments dated September 30, 2010, November 3, 2010, November 9, 2010, November 18, 2010, November 23, 2010, November 29, 2010, December 2, 2010, December 8, 2010, December 10, 2010, December 15, 2010, December 17, 2010, December 22, 2010, December 23, 2010, January 7, 2011, January 14, 2011, January 20, 2011, January 21, 2011, January 24, 2011, January 25, 2011, January 28, 2011, February 1, 2011, February 4, 2011, February 7, 2011, February 8, 2011, February 14, 2011, February 15, 2011, February 17, 2011, February 18, 2011, February 23, 2011, March 1, 2011, March 9, 2011, March 10, 2011, March 11, 2011, March 15, 2011, March 16, 2011, March 17, 2011, March 18, 2011, March 21, 2011, March 22, 2011, March 28, 2011, March 29, 2011, April 4, 2011, April 8, 2011, April 11, 2011, April 15, 2011, April 18, 2011, April 21, 2011, April 25, 2011, April 26, 2011, April 28, 2011, April 29, 2011, May 3, 2011, May 4, 2011, May 5, 2011, May 6, 2011, May 9, 2011, May 10, 2011, May 11, 2011, May 12, 2011, and May 13, 2011.

This new drug application provides for the use of VICTRELIS™ (boceprevir) 200 mg capsules for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients, 18 years of age and older, with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

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.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 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 11, 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 202258**." 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:

Sherly Abraham
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6369
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

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

Sherly Abraham
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6369
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 and very few patients aged 0 to under 3 years with CHC require treatment.

We are deferring the pediatric studies 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 under 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.

1767-1 Conduct a single-dose pharmacokinetics study of boceprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine weight-based dosing for children that will result in exposures similar to those observed in adults.

Final Protocol Submission:	July, 2011
Trial Completion:	February, 2013
Final Report Submission:	May, 2013

1767-2 Conduct a trial to evaluate safety and treatment response of boceprevir 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 boceprevir, including growth assessment and sexual maturation in pediatric subjects, to determine the durability of response and to characterize boceprevir resistance-associated substitutions.

Final Protocol Submission: February, 2012
Trial Completion: July, 2015
Final Report Submission: October, 2015
Long-term Final Report Submission: November, 2020

Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study 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 identify the unexpected serious risks of drug interactions with certain important medications for the intended patient population. Also, additional information is required to characterize the emergence and long-term persistence of boceprevir resistance-associated substitutions following treatment failure, to assess the impact of specific HCV amino acid substitutions on viral susceptibility to boceprevir in a cell culture model, and to evaluate the potential effects of boceprevir resistance-associated substitutions on boceprevir efficacy in treated patients.

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 this serious risk.

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

Virology

1767-3 Conduct a study to assess the impact of boceprevir treatment-emergent NS3 amino acid substitutions (those that have been observed but not characterized phenotypically) on the anti-HCV activity of boceprevir in the HCV replicon system. Potentially novel resistance-associated substitutions should also be

evaluated. The HCV replicon genotype/subtype background used should be consistent with the background in which the specific substitutions have been observed in treated patients. Evaluations should include HCV replicons with previously characterized resistance-associated substitutions spanning the range of susceptibilities as reference standards. Specific examples of substitutions to be assessed include the following:

a. D168N, with and without linked R155T, genotype 1a replicon
b. V107I, with and without linked V36M+R155K, genotype 1a replicon
c. P146S, with and without linked V36M+R155K, genotype 1a replicon
d. I170V, genotype 1a replicon
e. V36M, R155K and V36M+R155K, genotype 1a replicon

The timetable you submitted on May 10, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June, 2011
Study Completion:	June, 2012
Final Report Submission:	July, 2012

1767-4 Conduct pooled analyses to characterize the impact of detectable baseline boceprevir resistance-associated polymorphisms on the efficacy of boceprevir + Peg-IFNα/RBV treatment regimens among subjects who (1) respond relatively poorly to the Peg-IFNα/RBV 4-week lead-in (e.g., <1 $\log_{10}$ IU/mL decline, ≥ 1 $\log_{10}$ IU/mL to <2 $\log_{10}$ IU/mL decline, etc.), or (2) have an unfavorable IL28B genotype (if data are available). These pooled analyses should be conducted using data from the following completed and currently ongoing boceprevir clinical trials: P03523, P05216, P05101, P05411, P05685, and P06086. These analyses should be completed, and a study report submitted, within 9 months of collection of SVR outcome data from these clinical trials.

The timetable you submitted on May 10, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	August, 2011
Final Report Submission:	April, 2013

1767-5 Conduct a study to analyze NS3/4A protease cleavage sites for the presence of boceprevir treatment-emergent substitutions for a selected subset of subjects (n~10) representative of the virologic failure responses and NS3 protease resistance patterns observed in Phase 3 trials. An additional subset of subjects (n~10) who experienced virologic failure, but for whom no clear resistance-associated substitutions in NS3/4A were detected, should also be analyzed for the presence of boceprevir treatment-emergent substitutions in NS3/4A protease cleavage sites.

The timetable you submitted on May 10, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June, 2011
Study Completion:	March, 2012
Final Report Submission:	July, 2012

1767-6 Report results from ongoing clinical trial P05063 regarding the long-term persistence of amino acid substitutions that emerged in boceprevir-treated subjects from the following Phase 2 and Phase 3 trials conducted to date: P03523, P03659, P05216 and P05101. For long-term, follow-up analyses of subjects from the Phase 3 trials (P05216 and P05101), if available, the same assay/vendor used initially to identify the treatment-emergent substitutions should continue to be used to monitor the persistence of the substitutions in the follow-up period. The persistence of detectable amino acid substitutions should be assessed for a treatment-free follow up period of approximately 2 years.

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	July, 2011
Trial Completion:	December, 2011
Final Report Submission:	July, 2012

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to identify the unexpected serious risks of drug interactions with certain important medications for the intended population and of potential effects of boceprevir resistance-associated substitutions on boceprevir-based treatment efficacy.

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

Clinical Pharmacology

1767-7 Conduct an *in vivo* drug-drug interaction trial between boceprevir and an oral contraceptive containing a progesterone component other than drospirenone.

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	July, 2011
Trial Completion:	February, 2012

Final Report Submission: July, 2012

1767-8 Conduct an *in vivo* drug-drug interaction trial between boceprevir and methadone.

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: May, 2011
Trial Completion: September, 2011
Final Report Submission: March, 2012

1767-9 Conduct an *in vivo* drug-drug interaction trial between boceprevir and a sensitive substrate of p-glycoprotein (*e.g.* digoxin).

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: July, 2011
Trial Completion: December, 2011
Final Report Submission: April, 2012

1767-10 Conduct an *in vivo* drug-drug interaction trial between boceprevir and a selective serotonin reuptake inhibitor (SSRI) (*e.g.* escitalopram).

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: June, 2011
Trial Completion: December, 2011
Final Report Submission: July, 2012

Submit the protocols to your IND 69,027, with a cross-reference letter to this NDA. Submit all final reports to this 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 Pharmacology

1767-11 Conduct an *in-vivo* drug-drug interaction trial between boceprevir and tacrolimus.

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	May, 2011
Trial Completion:	August, 2011
Final Report Submission:	January, 2012

1767-12 Conduct an *in-vivo* drug-drug interaction trial between boceprevir and cyclosporine.

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	May, 2011
Trial Completion:	September, 2011
Final Report Submission:	February, 2012

1767-13 Conduct an *in vivo* drug-drug interaction trial between boceprevir and prednisone.

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December, 2011
Trial Completion:	March, 2012
Final Report Submission:	August, 2012

Clinical

1767-14 Conduct a trial evaluating shorter treatment durations of pegylated interferon and ribavirin (PR) with and without boceprevir in treatment-naïve patients with the IL28B rs12979860 C/C genotype.

The timetable you submitted on May 10, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November, 2011
Trial Completion:	April, 2014
Final Report Submission:	October, 2014

1767-15 Submit the final report and datasets for Study P05514 (PROVIDE), an open label ongoing efficacy trial in which boceprevir treatment in combination with peginterferon alfa and ribavirin is provided to subjects with chronic hepatitis C genotype 1 who did not respond to the peginterferon alfa and ribavirin control in previous boceprevir trials.

The timetable you submitted on May 12, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion:	June, 2013
Final Report Submission:	December, 2013

Virology

1767-16 Conduct a study to assess phenotypic susceptibility of baseline and treatment failure isolates from boceprevir-treated subjects (n~10) using the HCV replicon system. These analyses could focus on a subset of subjects whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials. Baseline isolates from a few boceprevir treated subjects (n~5) who achieved SVR should be included in these assessments for comparison. Entire NS3 protease or NS3/4A cassettes should be amplified from patient isolates and cloned into an appropriate HCV replicon vector for phenotypic characterization related to boceprevir susceptibility.

The timetable you submitted on May 10, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June, 2011
Study Completion:	June, 2012
Final Report Submission:	July, 2012

1767-17 Conduct analyses to identify potential mechanisms of persistence of viral populations harboring boceprevir treatment-emergent, resistance-associated substitutions, based on observations in clinical trial P05063. The potential role of compensatory amino acid substitutions or virologic failure category (e.g., breakthrough, non-response, relapse) on the long-term persistence of boceprevir resistance-associated substitutions should be investigated. Also, a subset of subjects (n ~20) whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials should have long-term, follow-up samples characterized genotypically using a sensitive and quantitative nucleotide sequencing assay to characterize the dynamics of the complex viral populations over 1 to 2 years of treatment-free follow-up.

The timetable you submitted on May 10, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June, 2011
Study Completion:	June, 2012
Final Report Submission:	September, 2012

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.

Submit clinical protocols to your IND 69,027 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study 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**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated November 10, 2010, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for VICTRELIS™ (boceprevir) 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 Sherly Abraham, R.Ph., Regulatory Project Manager, at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
Carton and 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
05/13/2011