CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202258Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: April 15, 2011

To: NDA 202-258

From: Terrance Ocheltree, Ph.D., R. Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 202-258, Victrelis™ (boceprevir) 200 mg capsule.

I have assessed the ONDQA reviews of NDA 202-258 by Mark Seggel, Ph.D. The ONDQA CMC review for this product was finalized on April 13, 2011 and the ONDQA Biopharmaceutics review was completed on April 08, 2001. ONDQA recommends **Approval** of this NDA. Sufficient information has been provided to assure identity, strength, purity and quality.

No post marketing commitments are proposed by ONDQA.

Boceprevir 200 mg capsule is an immediate release, red and yellow, hard gelatin capsule. The red opaque cap is printed with the Merck logo in yellow while the yellow body is printed with the product code ID "314" in red ink. The commercial configuration of the drug product is capsules supplied in cartons of twenty-eight (28) twelve (12) count bottles. Each bottle contains a single day's does (800 mg three times daily). Boceprevir capsules are recommended to be stored refrigerated (2-8ºC) for up to 24 months or until dispensed to the patient. Once dispensed, the capsule may be stored at room temperature for up to three (3) months. A 24 month expiry period is recommended based on the submitted stability data.

All manufacturing and testing facilities have acceptable site recommendations as of April 15, 2011, based on the Overall Recommendation made on March 16, 2011.

I concur with the "Approval" recommendation from an ONDQA perspective and the absence of ONDQA related post marketing commitments.

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/s/

TERRANCE W OCHELTREE
04/18/2011

NDA 202-258

Victrelis™
(boceprevir) Capsules
200 mg

Schering Corporation

Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-258

2. REVIEW #: 1

3. REVIEW DATE: 08-APR-2011

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Not Applicable	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
0000 Pre-submission (rolling NDA)	30-SEP-2010
0001 Original NDA	10-NOV-2010
0007 (Response to establishment IR)	08-DEC-2010
0019 (Response to FDA CMC Request)	26-JAN-2011
0041 (Response to information request)	21-MAR-2011
0043 (Response to CMC & Biopharmaceutics requests)	28-MAR-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering-Plough Corporation [Merck]
Address:	2000 Galloping Hill Road Kenilworth, NJ 07033-0530
Representative(s):	Patricia Strasser, Manager Pharmaceutical CMC
Telephone:	908-740-2648

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Victrelis™
   b) Non-Proprietary Name (USAN): Boceprevir
   c) Code Name/#: SCH 503034; HCV-Y
   d) CAS Registry Number: 394730-60-0
   e) Chem. Type/Submission Priority:
      i. Chem. Type: 1
      ii. Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
_____SPOTS product – Form Completed

___X__Not a SPOTS product

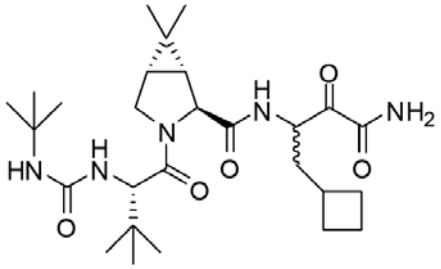
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

CAS Chemical Name: (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(S)-carboxamide

IUPAC Chemical Name: (1R,2S,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-{N-[(tert-butyl-amino)carbonyl]-3-methyl-L-valyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

USAN: Boceprevir

Structural Formula:



Molecular Formula: $C_{27}H_{45}N_5O_5$

Molecular Weight: 519.7

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted] (b) (4)	III	[redacted]	(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		

[1] Action c
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	DOCUMENT
IND 69,027	Boceprevir for treatment of HCV	All

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable	-	
EES	Acceptable	16-MAR-2011	M. Toulouse, Office of Compliance
Pharm/Tox	Qualification of impurities Assessment of [redacted] (b) (4) impurity	13-MAR-2011	C. Ellis and H. Ghantous, DAVP
ONDQA Biopharmaceutics	Approval recommended	08-APR-2011	M. Seggel, ONDQA (see separate ONDQA Biopharmaceutics review)
LNC	Not applicable	-	
Methods Validation	Not applicable	-	
DMEPA	Trademark acceptable *No comments on labels to date.*	15-FEB-2011	J. Abdus-Samad, DMEPA
EA	Categorical exclusion acceptable	21-MAR-2011	M. Seggel, ONDQA
Quality Microbiology	Not applicable	-	

19. GOAL DATES

GRMP Goal: 15-APR-2011
PDUFA Goal: 13-MAY-2011

The Chemistry Review for NDA 202-258

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient information to assure identity, strength, quality, purity, potency and bioavailability of the drug product. The labels have adequate information as required. The Office of Compliance has issued an overall recommendation of 'Acceptable' based on the satisfactory cGMP status of the manufacturing facilities. Therefore, from the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Victrelis™ hard gelatin capsules contain 200 mg of boceprevir, a reversible, covalent inhibitor of the hepatitis C virus (HCV) non-structural protein 3 (NS3) serine protease. The electrophilic ketoamide group of boceprevir functions as a trap for the catalytic serine hydroxyl group. Boceprevir is a BCS Class IV drug (low solubility [1.5 mg/mL], low permeability).

Victrelis also contains microcrystalline cellulose, lactose monohydrate, pregelatinized starch, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate in an immediate release formulation. All are commonly used pharmaceutical excipients. Sodium lauryl sulfate (SLS) is an anionic surfactant added (b) (4)

The capsule content is (b) (4) Although 'Quality by Design' (QbD) is not mentioned, the applicant has described in detail the manufacturing process development, including Design of Experiments (DoE), establishment of Normal Operating Ranges (NOR) and Proven Acceptable Ranges (PAR), Critical Quality Attributes (CQA) and Critical Process Parameters (CPP). No CPP were identified. As the applicant notes, (b) (4)

Numerous commercial process/site batches have been manufactured in support of this application. Analytical tests include identification (by IR), moisture content, assay, and determination of the various degradation products that may be present (Degradation Products Group A, Degradation Product Group B, Dimers [the primary class of degradants observed in boceprevir] and totals). Although the impurity profile and degradation profile of boceprevir (see below) and the drug product are fairly complex, the applicant has successfully characterized the origins and conditions for formations of the impurities and degradants. Acceptance criterion for individual specified impurities (degradants), subtotals, and total degradants have been proposed. Totals for Group A and Group B degradants are limited to (b) (4) and while totals for each group typically are less than half that amount, the limits seem reasonable given the overall complexity of the impurity/degradation profile. Individual Dimers are limited to NMT (b) (4) Total Dimers are limited to (b) (4). Total degradants are limited to not more than (b) (4) over the shelf-life of the product. Totals in 18 Phase III batches did not exceed (b) (4) at release. Significant degradation has not been observed under the long term condition of 5°C. Nevertheless, based on the totality of the available information regarding the potential formation of degradants, the lack of specific toxicological concerns, and given the overall risk-benefit of the drug product tightening of the acceptance criteria does not seem to be warranted at this time.

The applicant has agreed to a dissolution test acceptance criterion of Q = (b) (4) at 60 minutes (see this reviewer's separate Biopharmaceutics review).

To reduce potential degradation the drug product is stored at 5°C before dispensing to patients. At 5°C there is no significant degradation, although there is some increase in dimers. Stability at 25°C supports the storage of the product at room temperature by patients for up to 3 months.

Boceprevir is manufactured by a (b) (4)

Unlike the description of drug product process development, the discussion of drug substance process development and controls is very brief. Only one CPP was identified across the first 2 stages. On the other hand, several CPP were identified for steps in (b) (4)

(b) (4)

(b) (4)

. In addition, a number of impurities may be considered qualified by virtue of the fact that they are also potential metabolites. While the available release and stability data could be used to justify tightening the acceptance criteria for individual and total impurities, given the relative complexity of the impurity and degradation pathways, the absence of toxicological concerns, and the overall benefit of the drug, revision of the drug substance specification is not warranted at this time.

Four analytical procedures have been developed in order to fully analyze the range of impurities in the drug substance.

Because of the potential toxicity of (b) (4) After extensive discussions with the Pharm/Tox review team, it was agreed that a limit of (b) (4) (b) (4)) was acceptable (see sections S.2.6, S.4.4 and S.4.5 for further discussion regarding (b) (4).

A retest period of (b) (4) proposed for drug substance stored under refrigeration based on long-term and accelerated stability data.

B. Description of How the Drug Product is Intended to be Used

Victrelis™ is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with pegylated interferon alpha and ribavirin, in adult patients (≥18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy.

Four capsules of boceprevir (800 mg) are administered three times a day for up to (b) (4) The drug product is supplied cartons of twenty-eight 12-count HPDE bottles, each bottle containing one day's dose.

Prior to dispensing, the drug product is to be stored refrigerated (2-8°C). Once dispensed to the patient, the product can be stored for up to 3 months at room temperature.

The refrigerated drug product has a 24-month expiration dating period.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendations. An inspection of Merck's Las Piedras, Puerto Rico facility for finished dosage form packaging and stability testing was completed; there were no significant observations. The Schering-Plough/ Merck drug substance and drug product manufacturing facilities in Singapore have acceptable cGMP based on profile class and file review. A product packaging facility in North Carolina also has acceptable cGMP status based on profile class. An overall recommendation of Acceptable was issued by the Office of Compliance on 16-MAR-2011 (see EES Report).

All labels have the required information. The proposed trademark, Victrelis, has been found acceptable by DMEPA. An assessment of container and carton labeling by DMEPA is pending.

III. Administrative

A. Reviewer's Signature

{see electronic signature page}

B. Endorsement Block

{see electronic signature page}

C. CC Block

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/s/

MARK R SEGGEL
04/12/2011

STEPHEN P MILLER
04/13/2011
I concur - this NDA is recommended for approval from the CMC perspective

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 202-258
Supplement Number and Type: Original
Established/Proper Name: Victrelis™ Boceprevir Capsules, 200 mg
Applicant: Schering Corporation
Letter Date: 10-NOV-2010 (eSub)
Stamp Date: 15-NOV-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		eCTD submission
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		0001 FDA Form 356h
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			Not applicable

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		as revised 08-DEC-2010
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		as revised 08-DEC-2010

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		as revised 08-DEC-2010
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		Ready 10-NOV-2010

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion: EIC less than 1 ppb

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		three primary/site stability batches (ongoing) 12 months @ 5°C provided 6 months @ 25°C/60% RH provided one supportive batch 18 months @ 5°C 12 months @ 25°C/60% RH 6 months @ 30°C/75% RH 3 months @ 40°C/75% RH proposed retest period (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?		X	executed batch records for one clinical/primary site stability batch (K-H09700) and one market image site-stability batch (K-H10354) no proposed master batch record
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		See 3.2.P.2.2
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		12-count, 30-mL HDPE bottles with CR (b) (4) closures with induction seals
25.	Does the section contain controls of the final drug product?	X		

26.	Has stability data and analysis been provided to support the requested expiration date?	X		3 primary/site stability batches: 12 months @ 5°C 6 months @ 25°C/60% RH 3 months @ 40°C/75% RH 3 commercial image/site stability batches 6 months @ 5°C 6 months @ 25°C/60% RH supportive stability batch: 24 months @ 5°C 6 months @ 25°C/60% RH simulated use: 6 months @ 25°C/60% RH 3 months @ 40°C/75% RH (after long term at 5°C) proposed expiry 24 months @ 5°C + 3 months ambient room temperature
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Not applicable

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	2/17/2010	
	III			3/16/2010	
	III			3/30/2010	
	III			3/30/2010	
	IV			10/7/2010	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	No filing comments
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	pending completion of IQA

{See appended electronic signature page}

Mark R. Seggel

{See appended electronic signature page}

Stephen P. Miller, PhD, Branch Chief

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

/s/

MARK R SEGGEL
12/09/2010

STEPHEN P MILLER
12/09/2010