CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	202-258
Applicant Name	Schering Corp.
Date of Submission	11/15/2010
PDUFA Goal Date	5/15/2010
Proprietary Name / **Established (USAN) Name**	Victrelis boceprevir
Dosage Forms / Strength	capsule / 200 mg
Proposed Indication	Boceprevir is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Poonam Mishra, Sarah Connelly, Charles Cooper
Statistical Review	Wen Zeng, Greg Soon
Pharmacology Toxicology Review	Christopher Ellis, Hanan Ghantous, Abigail Jacobs
CMC Review/OBP Review	Mark Seggel, Steve Miller, Terrence Ocheltree
Microbiology Review	Patrick Herrington, Jules O'Rear
Clinical Pharmacology Review	Ruben Ayala, Jeff Florian, Shashi Amur, Michael Pacanowski, Pravin Jadhav, Sarah Robertson,
DDMAC	Lynn Panholzer, Michael Safarik
DSI	Antoine El- Hage, Tejashri Purohit-Sheth
CDTL Review	Mary Singer
OSE/DMEPA	Jabril Abdus-Samad, Todd Bridges, Carol Holquist
OSE/DRISK	Steven Morrin, Barbara Fuller, LaShawn Griffiths
DRUP Consultation	Gerald Willet
IRT QT review	Joanne Zhang, Janice Brodsky, Joo Yeon Lee, Hao Zhu, Monica Fiszman, Norman Stockbridge
Hematology Consultation	Andrew Dmytrijuk, Kathy Robie Suh
Divisional Review	Jeff Murray

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Background

Boceprevir is an inhibitor of the hepatitis C virus NS3/4A protease. The NS3/4A protease is responsible for cleaving an HCV polyprotein to produce mature protein components, as part of the viral replication cycle. Boceprevir is the first direct acting antiviral submitted for treatment of chronic hepatitis C; it has not received marketing approval outside of the US to date. NDA 202-258 studies boceprevir in combination with peginterferon alfa and ribavirin (PR) for the treatment of chronic hepatitis C virus infections, genotype 1a and 1b, in patient who are treatment naïve and who have failed prior therapy. The clinical trials were designed to show superiority of boceprevir in combination with PR over PR. Peginterferon alfa in combination with ribavirin is an approved regimen for the treatment of chronic hepatitis C virus infection.

The prevalence of chronic hepatitis C virus infection in the US is estimated to be approximately 3.2 million persons. For those infected with hepatitis C, it is estimated that 75 to 85 % of patients will go on to develop chronic infection, 60 to 70 % will over time develop chronic liver disease, 5 to 20% will develop cirrhosis during the period of 20 to 30 years after infection, and 1 to 5% will die from the chronic hepatitis C infection from sequelae such as hepatocellular carcinoma or cirrhosis.

In the US, genotype 1 is the most prevalent of the six genotypes of hepatitis C virus (HCV). As noted in the product labeling for PegIntron (peginterferon alfa-2b), subjects with genotype 1 that received PR had lower rates of achieving sustained virologic response at 24 weeks compared to patients with other hepatitis C viral genotypes. Boceprevir has only been studied in patients with chronic HCV genotype 1 infection. In a biochemical assay, the activity of boceprevir against a NS3/4A protease from single isolates of hepatitis C virus genotypes 2 and 3a were reduced by 2 to 3 fold.

The endpoint utilized in the phase 3 trials of boceprevir was Sustained Virologic Response at 24 weeks after completion of therapy (SVR24) defined as HCV RNA levels below the limit of detection.[1] As noted in our draft Guidance document on developing direct acting antiviral agents for hepatitis C infection, we utilize SVR 24 as a clinically validated endpoint for chronic hepatitis C infection based upon evaluation of data from observational studies. In addition, a recent review article also supports the role of SVR as a validated endpoint for assessing treatment of chronic hepatitis C virus infection.[2]

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of boceprevir for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy. For a detailed discussion of NDA 202-258, the reader is referred to the individual discipline specific reviews. In addition Dr. Singer's Cross-Discipline Team Leader

[1] Review of results for HCV RNA below the limit of detection found infrequent positive results that are likely to be false positives. Hence, we utilize below the limit of quantitation in the product labeling to describe results for SVR.
[2] Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis. 2011 Apr 1;52(7):889-900.

Memorandum and Dr. Murray's Deputy Division Director's Memo summarize key issues in the NDA submission. I concur with the recommendations of the review team that the information on safety, efficacy and product quality for boceprevir support approval. This memorandum will focus on selected issues from the application.

Chemistry Manufacturing and Controls

The chemistry manufacturing and controls are summarized in Dr. Seggel's Chemistry review which recommends approval from the standpoint of CMC for boceprevir 200 mg capsules, a hard gelatin capsule. The capsules have a 24 month expiry dating when stored at 2-8°C and can be stored for 3 months at room temperature after dispensing. The Office of Compliance has issued a recommendation of Acceptable for the manufacturing and testing facilities.

Pharmacology Toxicology

The recommendation from Dr. Ellis with regards to the pharm/tox studies is for approval from a pharm/tox standpoint. In studies in cynomologous monkeys mild anemia with increased retilculocytosis were noted at exposures 1.9-fold the human exposure based upon AUC. The effects on anemia did not progress over a 3 month period of time. Boceprevir was not found to be mutagenic or clastogenic and in 2-year rat and mouse carcinogenicity studies was not associated with drug-related neoplasms. The carcinogenicity study was reviewed by the Executive Carcinogenicity Committee and found (1) to be an adequate study and (2) that no drug-related tumors were observed. Boceprevir is administered in combination with peginterferon alfa (has abortifacient effects) and ribavirin (has teratogenic and/or embryocidal effects) and hence is labeled as Pregnancy Category X.

Virology

The virology assessment of boceprevir is discussed in Dr. Harrington's virology review. His recommendation is for approval. Boceprevir acts by inhibiting the enzymatic activity of the HCV NS3/4A protease that cleaves the HCV nonstructural polyprotein, a step in the viral replication cycle of HCV. Analyses of treatment emerging mutations in boceprevir-treated patients who did not achieve SVR identified several mutations in genotype 1a and genotype 1b HCV. The information on treatment emergent mutations in genotype 1a and genotype 1b are presented in the label grouped by frequency at which a particular amino acid change was observed. In addition, there are also recommendations provided for additional studies to be performed post-approval to further evaluate resistance mutations for boceprevir.

Clinical Pharmacology

The clinical pharmacology of boceprevir is discussed in Dr. Ayala's Clinical Pharmacology Review. He finds that the material in the NDA is acceptable for approval and notes that additional drug-drug interaction studies should be conducted post-approval.

The usual adult dose of boceprevir is three 800 mg doses taken orally at 7-9 hour intervals. Dr. Ayala's notes that boceprevir should be taken with food. Dose adjustment is not needed based upon renal impairment, hepatic impairment, age, gender, race, body weight. Boceprevir is a strong inhibitor of CYP3A4 and a substrate of CYP3A4. Boceprevir is also a substrate for P-gp and may be an inhibitor. The product label provides information on drug interactions and notes concomitant medications that are contraindicated and other significant drug interactions. Also noted is that boceprevir leads to reduction in ethinyl estradiol which may lead to reduced effectiveness for oral contraceptives. An additional study will be conducted to further characterize interactions with oral contraceptives and cautionary wording will be included in the product labeling.

Exposure-response analysis for boceprevir found a relationship between increasing exposure and increasing anemia. Pharmacometric analyses were performed that evaluate the duration of therapy based upon response at (the presence or absence of detectable HCV RNA) at week 8 and week 12 or 24. The results of these analyses, along with considering the risks and benefits of boceprevir + PR treatment have been considered in the dosing recommendations provided in the product labeling. In addition, an exploratory analysis of IL28B gene polymorphisms (this gene encodes for interferfon-lambda) found that C/T and T/T genotypes had higher SVR rates when receiving boceprevir + PR compared to PR alone. For treatment naïve patients with the CC genotype, response rates were similar in the presence or absence of boceprevir (all patients received PR).

A thorough QT study was conducted at doses of 800mg TID or 1200mg TID (supratherapeutic dose) and found that boceprevir did not prolong the QT interval beyond the threshold for regulatory concern. The study was reviewed by the Interdiscplinary Review Team for QT studies and was judged to have assay sensitivity based upon the positive findings for the moxifloxacin control.

Clinical Efficacy and Safety

The results of the clinical trials evaluating the safety and efficacy of boceprevir are discussed in detail in Dr. Mishra's and Dr. Connelly's Clinical Review, Dr. Zheng's Statistical Review, Dr. Singer's CDTL review and Dr. Murray's Deputy Division Director Review. The reader is referred to their reviews for a detailed discussion of safety and efficacy.

For the indication of treatment of chronic hepatitis C genotype 1 infection, in combination with PR, the applicant conducted two phase 3 trials. One trial was in patients who had not been previously treated and the other trial was in persons who had failed prior therapy.

Trial P05216 was a double-blind placebo controlled study comparing peginterferon alfa (PR) vs. response guided boceprevir therapy +PR vs. standard boceprevir therapy +PR (1:1:1) in patients who had not been previously treated. In Arm 1 (the PR control arm) patients received PR for 48 weeks duration. In the two boceprevir arms, there was an initial lead in period of 4 weeks of PR alone prior to starting boceprevir. Then in Arm 2 (Response Guided Therapy (RGT) boceprevir arm) boceprevir was added to PR for 24 weeks. For those patients that responded rapidly (HCV RNA negative at weeks 8 and 24), therapy was completed at week 28. For those that who were HCV RNA positive at week 8 (or any subsequent week prior to week 24) and negative at week 24, following completion of 24 weeks of boceprevir, they continued to receive an additional 20 weeks of PR. In Arm 3 of the trial, following the 4 week lead in phase, patients received PR and boceprevir for 44 weeks (48 weeks). For patients who remain HCV positive at 24 weeks, therapy was stopped for futility. The results of the trial are summarized in Table 1.

Table 1. P05216: SVR by Cohort and Treatment Arm

Study Cohorts	**Arm 1 PR48 (Control)**	**Arm 2 – RGT BOC/PR**	**Arm 3 BOC/PR48**
Cohort 1 Plus Cohort 2			
SVR % (n/N)	38 (138/363)	63 (233/368)	66 (242/366)
Relapse % (n/N)	22 (39/176)	9 (24/257)	9 (24/265)
Cohort 1 (non-Black)			
SVR % (n/N)	41 (126/311)	67 (211/316)	69 (213/311)
Cohort 2 (Black)			
SVR %	23 (12/52)	42 (22/52)	53 (29/55)

The results show that both boceprevir arms (Arm 2 and Arm 3) are statistically superior compared to the control arm (Arm 1) that received PR alone for 48 weeks. Results are also shown for Cohort 1 (non-black) and Cohort 2 (black) patients. There was an 11% lower response rate (not statistically significant) in the Cohort 2 patients that received RGT (Arm 2) compared to the cohort 2 patients that received boceprevir 44wk/ PR 48 wk (Arm 3).

Examination of the results for the subgroup of patients that received response guided therapy based upon virologic response at weeks 8 and 24 compared RGT to Arm 3 that received 44 weeks of boceprevir. The results show a 9% decrement in response (not statistically significant) in the subgroup of patients of treatment naïve late responders who received RGT compared to those who received boceprevir for 44 weeks (Table 2).

Table 2. Trial P05216 ; SVR by TW8-24 Response Category and Treatment Arm

Response Category	**RGT SVR n/N (%)**	**BOC44 SVR n/N (%)**
	PR4/BOC+PR24	**PR4/BOC+PR44**
Early Responders	156/161 (97)	155/161 (96)
	PR4/BOC+PR24/PR20	**PR4/BOC+PR44**
Late Responders	45/68 (66)	55/73 (75)

Trial P05101 was a double-blind placebo controlled study comparing PR vs. response guided boceprevir therapy +PR vs. standard boceprevir therapy +PR (1:2:2) in patients who had failed previous treatment for chronic hepatitis C. In Arm 1 (the control arm) patients received PR for 48 weeks duration. In the two boceprevir arms, there was an initial lead in period of 4 weeks of PR alone, prior to starting boceprevir. Then in Arm 2 (Response Guided Therapy (RGT) boceprevir arm) boceprevir was added to PR for 32 weeks. For those patients that responded rapidly (HCV RNA negative at weeks 8 and 12), therapy was completed at week 36. For those who were HCV RNA positive at week 8 and negative at week 12, they continued to receive an additional 12 weeks of PR after completion of 32 weeks of boceprevir. In Arm 3 of the trial, following the 4 week lead in phase, patients received PR and boceprevir for 44 weeks (48 weeks). For patients who remained HCV positive at 12 weeks in any of the three arms, therapy was stopped for futility. The study included partial responders and relapsers, but excluded patients who were prior null responders. The results of the trial are summarized in Table 3.

Table 3. P05101: SVR by Treatment Arm

Efficacy Parameter	**Arm 1 PR48 (Control)**	**Arm 2 RGT BOC/PR**	**Arm 3 BOC/PR48**
SVR % (n/N)	23 (18/80)	59 (96/162)	66 (107/161)
Relapse % (n/N)	28 (7/25)	14 (16/111)	12 (14/121)

Both boceprevir arms were statistically significantly superior to the control arm (Arm1), of PR alone. There was a numerical difference of 7% higher rate of SVR for the boceprevir 44 week + PR 48 week arm.

Although the numbers in each subgroup by treatment arm are quite small, the response rate in the subset of patients in trials P05216 and P05101 with cirrhosis are higher in the patients who received boceprevir 44 weeks along with PR following a 4 week lead in with PR.

Table 4. Trials P05216 and P05101: The Effect of Cirrhosis on Treatment Outcome

	Arm 1 PR 48 n/N (%)	**Arm 2 RGT n/N (%)**	**Arm 3 BOC/PR 48 n/N (%)**
P05216 (Naive)			
All Subjects	*138/363 (38)*	*233/368 (63)*	*242/366 (66)*
Cirrhosis			
NO	127/339 (38)	222/337 (66)	223/331 (67)
YES	6/13 (46)	5/16 (31)	10/24 (42)
P05101 (Experienced)			
All Subjects	*18/80 (23)*	*96/162(59)*	*107/161(67)*
Cirrhosis:			
NO	17/66 (26)	86/132 (65)	85/128 (66)
YES	0/10 (0)	6/17 (35)	17/22 (77)

The SVRs observed for patients in the boceprevir RGT arm compared to boceprevir 44 week arm for early responders (HCV RNA negative at weeks 8 and 12) and late responders (HCV RNA positive at week 8 but negative by week 12) is shown in Table 5. There are small numerical differences in SVR rates between the groups.

Table 5. Trial P05101 ; SVR by TW8-12 Response Category and Treatment Arm

Response Category	**RGT SVR n/N (%)**	**BOC44 SVR n/N (%)**
	PR4/BOC+PR32	**PR4/BOC+PR44**
Early Responders	61/68 (90)	68/70 (97)
	PR4/BOC+PR32/PR12	**PR4/BOC+PR44**
Late Responders	27/34 (79)	29/40 (73)

The results from studies P05216 and P05101 where superiority is demonstrated for the boceprevir containing arms over the control arms of PR alone provide evidence of the efficacy of boceprevir for the treatment of patients with chronic hepatitis C genotype 1 infection. Study P05101 did not include prior null responders and this should be noted in the product labeling.

Safety

Over 2000 subjects received boceprevir in combination with PR in phase 2 or 3 trials for a median duration of 201 days. The proportion of patient who discontinued study therapy was 13% for subjects receiving boceprevir and PR and 12% for patients receiving PR alone. Anemia occurred at a greater frequency in patients receiving boceprevir compared to patients receiving PR alone. In the boceprevir arms Hgb<10 g/dL was reported in 52% (547/1057) compared to 32% (141/443) of patients in the PR arm. Neutropenia and thrombocytopenia were also reported more frequently in patients receiving boceprevir compared to patients receiving PR alone. The labeling includes in the Warnings and Precautions statements on anemia and neutropenia and instructions for monitoring. In addition, a Contraindication statement that boceprevir use with peginterferon alfa and ribavirin is contraindicated in pregnant women and men whose female partners are pregnant. A Warning and Precaution statement is included regarding the teratogenic and embryocidal effects of ribavirin, the need for pregnancy testing before initiating therapy, pregnancy prevention, and the potential effects on hormonal contraceptives. The product label provides information on drug interactions and notes concomitant medications that are contraindicated and other significant drug interactions. In addition, a Medication Guide communicating these risks along with other information about treatment with boceprevir in combination with peginterferon alfa and ribavirin is also required.

The dosage and administration instructions in the product labeling are the result of careful consideration of the results from the clinical trials, patient response to therapy, analyses evaluating response to therapy based on patient characteristics, and consideration of the risks of longer vs. shorter course of therapy.

DMEPA / DSI Inspections / Pediatrics

DMEPA has consulted on the proprietary name and found it to be acceptable.

The Division of Scientific Investigations performed clinical inspections and overall found the data collected in support of the application to be reliable and acceptable.

Pediatric studies required under PREA have been waived for less than three years of age and deferred for the age group of 3 to 17 years as noted in the approval letter.

Advisory Committee

The boceprevir NDA was presented to the Antiviral Drugs Advisory Committee on April 27, 2011. The Committee first discussed safety and noted the increase in anemia events in boceprevir-treated patients compared to PR alone and also discussed neutropenia. They recommended that information be provided to communicate these risks. On the question of approval of boceprevir the Committee was unanimous, with a vote of 18 Yes; 0 No; and 0 abstain. Many on the Committee cited the advance in therapy for chronic hepatitis C that this agent will provide over current therapy. On the question of including null responders in the

label, the Committee opinion was mixed. They asked that information be provide re: subpopulations in the product labeling to guide therapy and recommended a number of studies to be conducted post-approval.

Postmarketing Study Requirements and Commitments

Postmarketing Requirements and Commitments include studies to further understand resistance to boceprevir, additional studies to evaluate drug-drug interactions, and evaluation of shorter durations of peginterferon with ribavirin in IL-28B C/C genotype in treatment naïve patients.

Summary

I concur with the assessment of the review team that substantial evidence of safety and efficacy has been provided for boceprevir for the indication of treatment of chronic hepatitis C genotype 1 infection in adult patients (≥ 18 years of age) with compensated liver disease, including cirrhosis who are previously untreated or who have failed previous interferon and ribavirin therapy. Adding boceprevir to the regimen of peginterferon alfa and ribavirin demonstrated superior SVR rates for the boceprevir containing arms compared to peginterferon plus ribavirin. The product labeling provides information to guide appropriate therapy and describes the risks and adverse effects of therapy. The approval includes postmarketing commitments for additional studies to evaluate drug interactions

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/s/

EDWARD M COX
05/13/2011