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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 #	201-917
Supplement #	
Applicant Name	Vertex Pharmaceuticals Inc.
Date of Submission	11/23/2010
PDUFA Goal Date	5/23/2011
Proprietary Name / Established (USAN) Name	Incivek telaprevir
Dosage Forms / Strength	tablets / 375mg
Proposed Indication	telaprevir, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated, including prior null responders, partial responders, and relapsers
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Russ Fleischer
Statistical Review	Thomas Hammestrom, Greg Soon
Pharmacology Toxicology Review	Mark Powley, Hanan Ghantous
CMC Review/OBP Review	George Lunn, Bogdan Kurtyka, Lin Qi, Stephen Miller, Christopher Hough, Sandra Suarez, Patrick Marroum
Microbiology Review	Lisa Naeger, Jules ORear
Clinical Pharmacology Review	Shirley Seo, Jiang Liu, Michael Pacanowski, Pravin Jadhav, Sarah Robertson
DDMAC	Jessica Fox, Michelle Safarik
DSI	Antoine El-Hage, Tejashri Purohit-Sheth
CDTL Review	Linda Lewis
OSE/DMEPA	Walter Fava, Carlos Mena-Grillasca, Carol Holquist
OSE/DRISK	Carolyn Yancey, Mary Willy, Claudia Karwoski
DRUP Consultation	Gerald Willet, Lisa Soule, Scott Monroe
IRT QT review	Joanne Zhang, Qianyu Dang, Jiang Liu, Hao zhu, Suchitra Balakrishnan, Norman Stockbridge
Dermatology Consultation	Brenda Carr
Divisional Review	Debbie Birnkrant

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

Telaprevir 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. Telaprevir has not received marketing approval outside of the US to date.

NDA 201-917 studies telaprevir 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 telaprevir 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 post therapy compared to patients with other hepatitis C viral genotypes.

The endpoint utilized in the phase 3 trials of telaprevir 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 telaprevir, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated, including prior null responders, partial responders, and relapsers. For a detailed discussion of NDA 201-917, the reader is referred to the individual discipline specific reviews. In addition Dr. Lewis's Cross-Discipline Team Leader Memorandum and Dr. Birnkrant's Division

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.

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 telaprevir 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. George Lunn's Chemistry review which recommends approval from the standpoint of CMC for telaprevir 375 mg tablets. The ONDQA Biopharmaceutics team has reviewed the dissolution specification and arrived at an agreed upon dissolution specification. The manufacturer has used a Quality by Design approach; Normal Operating Ranges and Proven Acceptable Ranges for steps in the manufacturing process have been determined. Manufacturing facility inspections have also recently been completed. As of May 19, 2011, the Establishment Evaluation report for the manufacturing facilities is Acceptable.

Pharmacology Toxicology

The recommendation from Dr. Powley with regards to the pharm/tox studies is for approval from a pharm/tox standpoint. The primary organs of toxicity in nonclinical studies were the hematopoietic system, the liver, and the male reproductive system. Telaprevir was not considered genotoxic and given a duration of administration of 12 weeks, carcinogenicity studies were not required. Incivek is used in combination with ribavirin and peginterferon alfa. Ribavirin is a Pregnancy Category X agent and the Incivek product labeling notes this. In addition, the labeling also includes a contraindication regarding use in women who are, or may become pregnant, or male partners of pregnant women.

Virology

The virology assessment of telaprevir is discussed in Dr. Naeger's virology review. Her recommendation is for approval. Telaprevir 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 telaprevir-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 telaprevir.

Clinical Pharmacology

The clinical pharmacology of telaprevir is discussed in Dr. Seo's and colleagues' Clinical Pharmacology Review. She finds that the material in the NDA is acceptable.

The usual adult dose of telaprevir is two 375 mg tablets taken orally every 7-9 hours. The pharmacokinetics of telaprevir are non-linear, time-dependent, and population specific. Food was found to effect the bioavailability of telaprevir with a 3 to 4 fold higher AUC and C_{max} when administered in the fed state; the label notes that telaprevir should be taken with food. CYP3A4 is the main CYP isoform involved in telaprevir metabolism. The label provides information on drug interactions and contraindicated combinations or dosage adjustment due to drug interactions.

A thorough QT study was conducted and found that telaprevir did not prolong the QT interval beyond the threshold for regulatory concern. At a dose of 1875 mg the maximum placebo-adjusted QTcF mean increase was 7.0 msec [90% CI: 4.2-9.9]. The study was reviewed by the Interdisciplinary 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 telaprevir are discussed in detail in Mr. Fleischer's Clinical Review, Dr. Hammerstrom's Statistical Review, Dr. Lewis's CDTL review and Dr. Birnkrant's Division Director's 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 three phase 3 trials. Two trials were in patients who had not been previously treated and the third trial was in persons who had failed prior therapy.

Trial 108 was a randomized (1:1:1), double-blind, placebo controlled study comparing peginterferon alfa (PR) for 48 weeks vs. PR plus telaprevir for the first 8 weeks of therapy and PR for 24 or 48 weeks depending on virologic response (T8/PR) vs. PR plus telaprevir for the first 12 weeks of therapy and PR for 24 or 48 weeks depending on virologic response (T12/PR) in 1088 patients who had not been previously treated. The overall SVR rates for each of the arms were PR 46%; T8/PR 72%; T12/PR 79%. The telaprevir containing regimens were superior to the PR regimen; a higher point estimate was observed in the T12/PR regimen. Subjects who achieved an undetectable HCV RNA at weeks 4 and 12, were treated with 24 weeks of PR. In the T12/PR arm 58% of patients had an undetectable HCV RNA at weeks 4 and 12, whereas 8% of patients in the PR48 arm had an undetectable HCV RNA at weeks 4 and 12. There were a limited number of Black/African American patients and patients with cirrhosis at baseline. The 21 subjects with cirrhosis who received T12/PR had an overall SVR rate of 62%. In the 26 subjects who Black/African Americans, the overall SVR rate was 62%.

Trial 111 was a randomized, open-label trial designed to compare a regimen of telaprevir for 12 weeks plus 24 weeks of PR vs. telaprevir for 12 weeks plus 48 weeks of PR in 540 treatment naïve patients who were HCV RNA negative at 4 and 12 weeks. The SVR rates by treatment arm in those achieving negative HCV RNA at 4 and 12 weeks was 92% for the T12/PR24 arm compared to 90% for the T12/PR48 arm. Although the numbers were small, in patients with cirrhosis who were HCV negative at 4 and 12 weeks, SVR for the T12/PR24 regimen was 67% (12/18) vs. 92% (11/12) for the T12/PR48 regimen. In the limited number of Black/African American patients enrolled who became HCV negative at 4 and 12 weeks, SVR for the T12/PR24 regimen was 88% (15/17) vs. 94% (16/17) for the T12/PR48 regimen.

Trial C216 was a randomized (2:2:1), double-blinded, placebo controlled in 662 previously treated patients (prior relapsers, prior partial responders and prior null responders) that compared (1) T12/PR48 vs. (2) PR4 (lead-in phase) + T12/PR12+PR32 vs. (3) PR48. Each of the treatment arms included placebos to mask treatment assignment. The two telaprevir containing regimens produced similar SVR rates. The overall SVR rates for the pooled telaprevir arms were as follows: for prior relapsers, pooled telaprevir + PR arms 86% (246/286) vs. PR alone 22% (15/68); prior partial responders, pooled telaprevir + PR arms 59% (57/97) vs. PR alone 15% (4/27); prior null responders, pooled telaprevir + PR arms 32% (47/147) vs. PR alone 5% (2/37). In the subgroups of patients with cirrhosis at baseline, the SVR rates, although the numbers were small, favored telaprevir + PR combination therapy over PR alone.

The trials demonstrate the efficacy of the 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. In addition, the labeling will also include the following points to consider: (1) that telaprevir must not be administered as monotherapy and must only be prescribed with both peginterferon alfa and ribavirin; (2) that a high proportion of previous null responders (particularly those with cirrhosis) did not achieve a Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment with telaprevir combination treatment; and (3) that telaprevir efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes telaprevir or other HCV NS3/4A protease inhibitors.

Safety

The pooled safety database from phase 3 trials included 1797 T/PR-treated patients and 493 PR-treated patients. The proportion of patients who discontinued study therapy was 14% for T/PR-treated patients compared to about 3% for PR treated patients. Serious adverse drug reactions occurred in 3% of T/PR-treated patients compared to none of the PR-treated patients. Skin disorders (rash and/or pruritis) were the most common category of serious adverse drug reaction.

Rash was reported in 56% of T/PR-treated patients compared to 34% of PR-treated patients. Most rash was of mild to moderate severity. Severe rash was reported in about 1% of patients.

Serious skin reactions (Drug Rash with Eosinophilia Syndrome (DRESS) and Stevens-Johnson Syndrome (SJS)) were reported in less than 1% of patients and all patients were noted to have recovered after hospitalization. The applicant had a Dermatology Expert Panel that reviewed skin reactions. Their review and assessment of the skin reactions are also described in Dr. Carr's Dermatology Consult. The product labeling includes a Warning and Precaution statement on Serious Skin Reactions in addition to a Warning and Precaution statement on Rash. These adverse reactions are also discussed in the Medication Guide that will accompany telaprevir. Serious Skin Reactions will be an adverse event that is followed closely during the postmarketing period. The applicant will submit all serious skin reactions as 15-day reports.

Anemia occurred at a greater frequency in patients receiving telaprevir compared to patients receiving PR alone. In the telaprevir arms, Hgb<10 g/dL was reported in 36% compared to 17% of patients in the PR arms. The product labeling includes a Warnings and Precautions statement on Anemia. Monitoring of Hgb prior to starting therapy and then every 4 weeks during therapy is recommended.

In addition, the labeling includes a Contraindications statement that telaprevir use with peginterferon alfa and ribavirin is contraindicated in pregnant women, women who may become pregnant, 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, the Medication Guide communicates these risks along with other information about treatment with telaprevir in combination with peginterferon alfa and ribavirin.

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 telaprevir NDA was presented to the Antiviral Drugs Advisory Committee on April 28, 2011. On the question of whether telaprevir should be approved the Committee voted Yes 18; No 0; and Abstain 0. The Committee discussion supported response guided therapy (length of therapy determined by presence or absence of early virologic response) in naive patients and to a lesser degree in prior relapsers, but some had questions about the quality of the data for prior relapsers. Some Committee members also cited phase 2 clinical trial data from 52 patients that

supported response guided therapy in prior relapsers. Regarding anemia, some Committee members noted that in the absence of use of erythropoietin stimulating agents they were able to understand the effects on anemia well. The Committee members discussed providing information that will help to educate regarding rash. The Committee also noted that adverse effects such as rash and anemia are expected and considering these risks, the Committee thought that the benefits of telaprevir therapy outweighed the risks. The dermatologist on the Committee also noted that more serious skin adverse events are likely to occur when the number of persons using the drug increases once the drug is marketed. The Committee recommended additional studies in Black/African American patients and patients with cirrhosis at baseline.

Postmarketing Study Requirements and Commitments

Postmarketing Requirements and Commitments include studies to further understand resistance to telaprevir, a study to evaluate proper dosing in patients on hemodialysis, clinical trials to further evaluate response in patients with cirrhosis and Blacks/African American patients and additional work to further evaluate for genomic factors that might be identified as risk factors for skin adverse events.

Summary

I concur with the assessment of the review team that substantial evidence of safety and efficacy has been provided for telaprevir 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 telaprevir to the regimen of peginterferon alfa and ribavirin demonstrated superior SVR rates for the telaprevir containing arms compared to peginterferon plus ribavirin. The product labeling provides information to guide appropriate therapy and the labeling and Medication Guide describe the risks and adverse effects of therapy.

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/s/

EDWARD M COX
05/23/2011