CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Decisional Review for NDA 201917

Date	May 13, 2011
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 201917
Proprietary / Established (USAN) names	Incivek ™/telaprevir
Dosage forms / strength	375 mg tablets, two tablets every 7-9 hour with a meal that is not low fat
Proposed Indication(s)	For use in combination with pegylated interferon and ribavirin for the treatment of genotype 1 chronic hepatitis C (CHC) in adult patients who are treatment naïve or who have been previously treated
Action	Approval

1. **Introduction to Review:** This Division Director's memorandum summarizes prominent features of NDA 201917 for Vertex Pharmaceutical's Inc. New Drug Application (NDA) for telaprevir, a new molecular entity that is a potent, reversible, selective, linear peptidomimetic ketoamide inhibitor of the NS3-4A HCV serine protease, an enzyme that is essential for viral replication. This review will cover non-clinical and clinical areas; Chemistry, Manufacturing and Controls (CMC) will be mentioned briefly.

2. **Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Division of Scientific Investigations (DSI) Status:** Chronic hepatitis C is both a global and domestic problem. Globally WHO estimates that upwards of 180 million persons are infected. Domestically, it is estimated that up to 4 million are infected, the majority of whom do not know their status (U.S. NHANES Survey 1999-2002). While the incidence of hepatitis C has been decreasing in the United States, complications of CHC are increasing and are expected to peak in the next 10-20 years without more potent therapies. Currently, the standard of care (SOC) for the treatment of CHC genotype 1 patients, the most common genotype in the US, is pegylated interferon with ribavirin for 48 weeks. Response rates are based on sustained virologic response (SVR) defined in published literature as an absence of detectable HCV RNA in the serum using an assay with a sensitivity of at least 50 IU/mL 6 months after completion of therapy. Overall SVR rates are 40-52%, but even lower in difficult to treat populations such as Blacks and as low as 10-25% in retreated patients (AASLD Practice Guidelines, 2009).

   SVR is an important endpoint. Though a virologic endpoint, it has been clinically validated as recent reports summarized by Pearlman and Traub in

CID 2011 demonstrate that achieving an SVR is associated with a decrease in CHC complications including cirrhosis, hepatocellular carcinoma, liver-related mortality and overall mortality. Balancing SVR with toxicity is a goal of therapy. The current SOC is associated with serious toxicities including hematologic, neuropsychiatric, immunologic, infectious, dermatologic and others. In addition, ribavirin is genotoxic and teratogenic and pegylated interferon is an abortifacient. Telaprevir also contributes to toxicity when used in combination with SOC, so an important goal of therapy is to be able to reduce the overall treatment duration, limiting exposure and thereby limiting toxicities. Telaprevir's potency allows for shortening of therapy duration in certain populations when early virologic responses are used to guide therapy; this is referred to as response guided therapy or RGT and will be an important strategy for patient management.

Telaprevir was granted fast-track status and the NDA was submitted as a rolling submission. The final clinical portion was submitted on November 22, 2010 and received on November 23, 2010. This NDA received a priority 6-month review because the results of the clinical trials showed that telaprevir when added to SOC was superior to SOC, increasing SVR rates to over 30% above that achieved with current SOC. This met the definition of unmet medical need. As this was an NME with far-reaching results that will change the treatment paradigm of CHC treatment, this application was presented before the Antiviral Products Advisory Committee on April 28, 2011.

DSI audits were completed. Four clinical trial sites, two domestic and two foreign were audited as was Vertex Pharmaceuticals in Cambridge, MA. Sites adhered to applicable statutory requirements and FDA regulations governing the conduct of clinical trials and the protection of human subjects.

3. Chemistry/Manufacturing/Controls (CMC): Please see CMC reviews by Drs. Lunn, Qi, Kurtyka, Hough, and Suarez, ONDQA. CMC issues have been adequately addressed, however inspections are pending. The Applicant applied aspects of a Quality-by-Design approach to manufacturing. According to the chemistry review, there were adequate specifications provided for the drug substance and drug product. The final drug product is formulated as a 375 mg film-coated tablet with a shelf-life of 24 months at 25° C.

During the review of this application it was determined that the trade name, Incivek™ was acceptable. Further, OSE's review of the final presentation, i.e blister packs containing daily dosing in three individual blisters contained in one strip and packaged in a carton of seven strips with four cartons packaged in a 28-day box was found to be adequate. In addition, the DMEPA reviewer noted that there were no additional areas of needed improvement for minimization of the potential for medication errors.

4. Nonclinical Pharmacology/Toxicology: I am in agreement with the conclusions of the thorough pharmacology/toxicology review by Drs. Mark Powley and Hanan Ghantous that were based on single- and multiple-dose in vivo toxicology studies in multiple species and in vitro and in vivo genotoxicity studies. Oral bioavailability is species specific and reached 70-95% in dogs. Telaprevir is extensively metabolized by CYP 3A4 with three resultant metabolites including pyrazinoic acid.

Other pertinent findings in animal studies were used to guide monitoring in clinical trials and included the following: Pivotal 6- and 9- month repeat-dose studies in rats and dogs, respectively revealed that the primary target organs for toxicity were bone marrow/hematologic system and liver. Decreases were seen in red cell parameters that were accompanied by an increase in reticulocytes with splenic changes. Increases in liver weight were accompanied by increases in hepatic transaminases without elevations in bilirubin; in the rat, hepatocellular hypertrophy and single-cell hepatocellular necrosis were also seen whereas in the dog, increased liver weight was accompanied by histologic changes consistent with a reversible perivasculitis that may have limited-to-unknown relevance to humans. Vasculitis and other secondary effects consistent with canine polyarteritis were also noted for other organs in dogs.

Male rats developed gross and histologic findings in the testes. Male reprotoxicity findings appeared to affect preimplantation and post-implantation, but the contribution of female reproductive system toxicity cannot be ruled out. In phase 2 clinical trials, FSH, LH and inhibin B were measured and found to be comparable between telaprevir containing arms and control.

Following review of genotoxicity studies, it was determined that telaprevir was not genotoxic. Carcinogenic potential was not assessed because telaprevir is not deemed to be genotoxic and will only be used for 12 weeks.

5. Clinical Pharmacology/Pharmacometrics:
Clincal Pharmacology and Pharmacometrics reviews were conducted by Drs. Shirley Seo, Sarah Robertson, Jiang Liu, and Pravin Jadhav; Pharmacogenomics reviewers were Drs. Shashi Amur and Mike Pacanowski. They reviewed 15 drug interaction studies examining 22 drugs, including methadone, two hepatic impairment studies, one renal impairment study, two thorough QT studies, an ADME study, a food-effect study, nine phase 1 studies examining bioavailability of different formulations, 14 studies examining the metabolism of telaprevir and limited IL28B data collected retrospectively. Also, the review team examined six phase 2 studies and three

phase 3 studies. Exposure-response assessments focused on efficacy and telaprevir-associated anemia and rash.

Pertinent findings from the thorough clinical pharmacology, pharmacometrics and pharmacogenomics reviews are described below:

- Telaprevir appears to be absorbed in the small intestine; telaprevir's absorption is also influenced by P-gp transported efflux.
- Telaprevir is both a CYP3A4 inhibitor and substrate; telaprevir is also a P-gp inhibitor and substrate.
- Metabolites of telaprevir, including pyrazinoic acid, VRT127394 (the R-diasteromer) and VRT0922061 are found in > 10% of total drug-related material at steady-state following multiple dosing. Notably, levels of pyrazinoic acid are lower than levels seen with pyrazinamide.
- Telaprevir is up to 79% protein bound.
- Telaprevir is primarily excreted through feces; there is minimal elimination in the urine and dose adjustment is not required in renally impaired subjects. Use is limited to subjects with a creatinine clearance $\geq$ 50 mL/min because telaprevir has to be dosed with pegylated interferon and ribavirin, both of which are contraindicated in moderate and severe renal impairment.
- The half-life of telaprevir is 9-11 hours.
- Up to a 4-fold increase in AUC and Cmax of telaprevir was observed when telaprevir was administered as a 750 mg single dose with food as compared with fasting; telaprevir was administered with food in phase 2 and 3 clinical trials. Consequently, labeling will state that telaprevir should be taken with food.
- Based on the Applicant's popPK analyses across phase 2 and 3 studies, race, gender, and age were not found to be a significant covariates on telaprevir clearance.

Hepatic impairment studies were conducted in subjects with mild and moderate hepatic impairment. Per Dr. Seo's review, clearance of telaprevir in subjects with mild hepatic impairment did not significantly change as compared to healthy subjects and no dose adjustment will be recommended in labeling for this group. Unexpectedly, clearance was increased and exposure was decreased in subjects with Child-Pugh B relative to healthy subjects. Severe hepatic impairment subjects were not studied based on findings in the moderately impaired subjects. Telaprevir use will not be recommended for subjects with moderate-to-severe hepatic impairment. This is also in accordance with the pegylated interferon and ribavirin product labels for the same patient populations with decompensated disease.

Two thorough QT studies were conducted. The results were reviewed by CDER's Interdisciplinary Review Team (IRT). The IRT concluded that no

significant QTc prolongation effect was detected and no significant concentration-QT relationship was established.

Safety and activity of combinations of different treatment durations of telaprevir and pegylated interferon and ribavirin were evaluated in phase 2. In phase 3 studies, safety and efficacy of telaprevir dosed for 8 or 12 weeks along with a 24-48 week course of SOC were also examined. Based on review of this data as well as exposure-response analyses related to safety and efficacy, the review team concluded that the dose of telaprevir should be 750 mg every 7-9 hours with food. Durations of pegylated interferon and ribavirin depend on early viral kinetics and patient status.

Addressing exposure/response relationships for this antiviral drug, no exposure parameter was identified as the best predictor of efficacy or safety. Pharmacometrics reviewers found that the relationship between telaprevir exposure and endpoints such as SVR and others that describe viral kinetics were shallow and statistically non-significant. The relationship between telaprevir and rash was also shallow and non-significant, however, higher telaprevir exposures were associated with more anemia.

Labeling advises that specific drugs in the following drug classes are contraindicated with telaprevir use because they are highly dependent on CYP3A for clearance and they have a narrow therapeutic index (see table 3 in draft package insert): alpha-1 adrenoreceptor antagonists, antimycobacterials, ergot derivatives, GI motility agents, herbal products, HMG CoA reductase inhibitors, neuroleptics, PDE-5 inhibitors, sedative/hypnotics.

A retrospective subgroup analysis of IL28B results demonstrated that telaprevir, when added to SOC, increased SVR rates regardless of genotype in treatment naïve subjects and in those who had failed previous treatment. Results should be viewed with caution as sample sizes of individual patient groups were small. In addition there was limited representation of Blacks and other subgroups, therefore without full representation of hepatitis C infected subjects broad conclusions cannot be drawn.

6. Clinical Microbiology: Please see extensive review by Dr. Lisa Naeger including comments about the assay that was used and cut-offs for virologic endpoints. Dr. Naeger noted in her review that the following NS3 amino acid substitutions emerged in subjects who did not achieve SVR in the phase 3 trials: V36 M, A or L, T54A or S, R155K or T, A156S, T or V and D168N. It is important to note that substitutions at position D168 had not been previously reported to be associated with telaprevir resistance and are known to confer decreased susceptibility to macrocyclic NS3-4A protease inhibitors (b) (4).

Other pertinent findings include:

- V36M/A, T54A/S, R155K/T, A156Sand R155T + D168N amino acid substitutions have been shown to confer 4 to 25 fold reduced susceptibility to telaprevir.
- V36M + R155K and A156T or V have been shown to confer > 62 fold reduced susceptibility to telaprevir.
- Telaprevir-associated resistance substitutions were present at baseline in 5% of subject samples in the pooled phase 3 studies. While it is important to note that these substitutions were present at baseline, it is equally important to note that it is difficult to determine how the presence of these substitutions will impact response outcomes because of the limited data.
- More substitutions emerged in genotype 1a as compared to 1b in subjects receiving telaprevir which translates into more on-treatment virologic failure in genotype 1a as compared to 1b
- On-treatment virologic failure was also more frequent in prior null responders.
- Genotype 1a subjects without SVR predominately had V36M and R155K or the combination of these substitutions whereas genotype 1b subjects without SVR predominately had V36A, T54A/S and A156S/T/V variants.
- Telaprevir resistant variants diminish over time, in the absence of drug pressure, but persist following treatment failure, up to three years at very low levels; most telaprevir-resistant variants are less fit than wild-type. The long term impact is not known as there is no retreatment data.
- Treatment-emergent NS3 amino acid substitutions that emerged in telaprevir-treated subjects who failed to achieve an SVR showed reduced anti-HCV activity to other NS3-4A protease inhibitors in development. Cross-resistance to interferon and ribavirin is not expected.
- Although telaprevir has shown antiviral activity against genotypes 1, 2, 3 and 4 in cell culture, results from pilot studies conducted in non-genotype 1 subjects showed very limited clinical activity.
- Telaprevir has not demonstrated activity against HIV or hepatitis B virus.

SVR is tantamount to a cure. SVR rates are durable as seen in follow-up to phase 2 studies where only 2/361 patients with SVR followed for an additional 48 weeks had a late relapse. Similarly, in an interim analysis of that same observational study, Study 112, a 3-year ongoing follow-up study designed to assess durability of SVR and evaluate evolution of resistant variants after treatment, SVR was durable in 99% of subjects followed for 5 to 35 months following SVR.

7. **Clinical Efficacy/Statistical:** I am in agreement with the conclusions reached by Dr. Linda Lewis detailed in the Cross-Discipline Team Leader memorandum and the reviews by Russ Fleischer, Clinical Analyst and Drs. Tom Hammerstrom and Greg Soon, Biostatisticians. Efficacy and safety were based primarily on phase 2 and phase 3 studies. Phase 2 studies were conducted in treatment naïve and previous treatment failures. Phase 2 studies supported the conclusion that there was no advantage to more than 12 weeks of dosing with telaprevir in combination with pegylated interferon and ribavirin. Further, it was determined that a ribavirin-sparing regimen was not a good treatment strategy because it allowed for increases in breakthrough and relapse rates. Individualized treatment using response-guided therapy was also explored first in phase 2 and further evaluated in phase 3.

   Additional pertinent findings from phase 2 treatment experienced subjects were as follows:

   - Prior relapsers achieved the highest SVR rates with all regimens evaluated; this was not unexpected as this group retains interferon sensitivity.
   - 49/52 (94%) of prior relapsers who received T12/PR 24 and who had an extended rapid virologic response (eRVR) defined as below the limit of detection at weeks 4 and 12, achieved an SVR.

   Phase 3 trials 108 and 111 were conducted in adult treatment naïve subjects with genotype 1 and phase 3 trial C216 was conducted in previously treated adult subjects with genotype 1. Trial 108 was designed to answer the question whether telaprevir dosed for 8 or 12 weeks plus SOC for 24 weeks was better than SOC for 48 weeks. Response-guided therapy was also examined. Subjects who achieved an eRVR were dosed for a total of 24 weeks while subjects who did not achieve an eRVR were dosed for a total of 48 weeks; the control arm was pegylated interferon and ribavirin dosed for 48 weeks. Futility rules were also incorporated into the trial and will appear in labeling to minimize resistance development.

   Demographics and baseline characteristics were well balanced in trial 108. Both telaprevir regimens were statistically superior to SOC. SVR rates were 79% and 72% respectively for the T12 and T8 regimens, compared to an expected SVR rate of 46% in the SOC arm; the trial was not designed to examine non-inferiority between T12 and T 8 regimens. eRVR as achieved in approximately 60% of subjects randomized to the telaprevir regimens translated into SVR rates of 92% for T12 and 87% for T8. Relapse rates occurred at 8%, 10% and 34% for T8, T12 and PR, respectively. When examining efficacy in historically difficult-to-treat subgroups, such as Blacks (~ 9%), Latinos (~ 11%), and cirrhotics (~ 7%) SVR rates approximately 30% above SOC were seen when telaprevir was

added to the regimen. It is important to note that representation of these groups was limited in all trials, though the Applicant was strongly advised to address their inclusion in adequate numbers early in drug development.

In sum, a 24-week treatment regimen of pegylated interferon and ribavirin with 12 weeks of telaprevir is supported in naïve subjects with an eRVR. In subjects not achieving an eRVR, it is recommended to dose pegylated interferon and ribavirin for 48 weeks.

Trial 111 was a supportive trial and was designed to answer the response-guided question of whether 24 or 48 weeks of pegylated interferon with ribavirin would improve outcomes of a 12-week telaprevir-based regimen in subjects who achieved an eRVR. The trial was powered for non-inferiority with a pre-defined margin of 10.5%. 92% of subjects who achieved an eRVR who received the 24 week regimen compared to 90% of subjects who received the 48-week regimen had an SVR. Non-inferiority was met with a 2-sided 95% CI (-4.3%, +8.2%) and supported the conclusion that there was no advantage to dosing naïve subjects longer with pegylated interferon and ribavirin if they achieved an eRVR.

Treatment naïve cirrhotics had limited representation in Trials 108 (n=47/1267) and 111 (n=61/530). Specifically, in trial 111, SVR rates among those who achieved an eRVR were 67% for subjects who received a 24-week telaprevir-containing regimen compared to 92% among those who received a 48-week telaprevir-containing regimen. See Table 1. Thus, treatment naïve subjects with cirrhosis may benefit from an additional 36 weeks of pegylated interferon and ribavirin for a total treatment duration of 48 weeks (telaprevir for 12 weeks in combination with pegylated interferon and ribavirin for 48 weeks).

Table 1 Response Rates for Treatment-Naïve Subjects with Cirrhosis

	eRVR	eRVR + SVR
Study 108 (n=47/1267)		
T8/PR (n=26)	**11/26 (42)**	**7/11 (64)**
T12/PR (n=21)	**9/21 (43)**	**7/9 (78)**
Study 111 (n=61/530)		
T12/PR24 (n=18) **T12/PR48 (n=12)**	**30/61 (49)**	**12/18 (67)** **11/12 (92)**

Pivotal trial C216 examined telaprevir dosed for 12 weeks in combination with pegylated interferon and ribavirin for 48 weeks in a genotype 1 treatment experienced population consisting of prior relapsers, partial responders and null responders. It evaluated a 4-week lead-in of

pegylated interferon and ribavirin to examine the impact on relapse and resistance. Demographics and baseline characteristics were well balanced. As this was a population that previously failed SOC, more subjects had cirrhosis, ~ 25% compared to the trials in the naïve population. Prior response was defined as follows:

- **RELAPSER** – HCV undetectable at the end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up
- **PARTIAL RESPONDER** – greater than or equal to a 2 log reduction in HCV RNA at week 12, but not achieving HCV undetectable at the end of treatment with a pegylated interferon/ribavirin regimen
- **NULL RESPONDER** – less than a 2 log reduction in HCV RNA at week 12 of a pegylated interferon/ribavirin regimen

About 53% of the population were relapsers, 28% were null responders and 19% were partial responders. Similar treatment outcomes were seen with and without a lead-in. Pooling the data from the telaprevir arms (immediate versus delayed start of pegylated interferon with ribavirin) and comparing it to control, 86% versus 22% of subjects in the relapser group achieved an SVR, 59% versus 15 % achieved an SVR in the partial responder group and 32% versus 5% achieved an SVR in the null responder group. SVR among cirrhotic subjects was highest among relapsers, 87% versus 13% for a telaprevir-containing regimen compared to SOC. For null responders, SVR was low with and without telaprevir, 14% versus 10%, but numbers were small. See Table 2.

Table 2 Response Rates for Prior Treatment Failures with Cirrhosis

C216	T12/PR n=139	PR n=30
Null Responder	7/50 (14)	1/10 (10)
Partial Responder	11/32 (34)	1/5 (20)
Relapser	48/55 (87)	2/15 (13)

Although response-guided therapy was not studied in C216, arguments can be made to support the use of RGT based on eRVR in relapsers. Prior relapsers appear to most closely resemble naïve subjects based on interferon responsiveness. Data from phase 2 trials showed that prior relapsers with eRVR who received telaprevir for 12 weeks with pegylated

ribavirin for 24 weeks had an SVR greater than 90 % which is comparable to naives, though numbers are small.

8. **Safety:** Safety data were pooled across phase 2 and 3 trials because telaprevir had a similar safety profile in naïve and prior treatment failures. For the purposes of my comments, I will focus on the pooled data from the phase 3 studies, similar to what appears in labeling. It is important to note that telaprevir adverse events occur on top of adverse events seen with SOC.

   Before addressing the pooled data I wanted to comment on the pregnancy category description and use of birth control with a telaprevir-based regimen. This is slated to appear first in the Warnings and Precautions section of the label. Telaprevir is pregnancy category B. However it will be used with pegylated interferon and ribavirin; ribavirin is pregnancy category X. Since telaprevir will be dosed in combination with pegylated interferon and ribavirin, the contraindications and warnings applicable to SOC will need to be applied to a telaprevir-based regimen. Further telaprevir has a drug interaction with oral contraceptives such that when ethinyl estradiol (EE) coadministered with norethindrone was dosed in the presence of telaprevir, the AUC of EE decreased by 28% possibly rendering oral contraceptives ineffective in the presence of telaprevir. Of note, the clinical reviewer did not find any unintended pregnancies in the database nor did he find events of breakthrough bleeding. Wording in the warnings and precautions section of the label will state:

   Because telaprevir must be used in combination with peginterferon alfa and ribavirin, the contraindications and warnings applicable to those drugs are applicable to combination therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during treatment and for 6 months after all treatment has ended. Female patients should have monthly pregnancy tests during treatment and during the 6-month period after stopping treatment. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin [see Contraindications (4), Use in Specific Populations (8.1), and Patient Counseling Information (17.2)]. Refer also to the prescribing information for ribavirin.

   Female Patients
   Hormonal contraceptives may not be reliable during Incivek™ dosing and for up to two weeks following cessation of Incivek™ [see Drug Interactions (7)]. During this time, female patients of childbearing potential should use

2 non-hormonal methods of effective birth control including barrier methods or IUDs [see also Patient Counseling Information (17.2)].

The clinical reviewer's safety analyses are based on data pooled from phase 3 trials that included 1797 subjects who received telaprevir and 493 who received pegylated interferon and ribavirin. The most common adverse drug reactions occurring in subjects receiving a telaprevir-based regimen and occurring greater than 5% above the control group were anemia, pruritus, rash, nausea, diarrhea, vomiting, anorectal discomfort, dysgeusia and fatigue. Rash and anemia will be highlighted.

SERIOUS SKIN REACTIONS/RASH

Rash, similar in character to that seen with pegylated interferon and ribavirin was identified in phase 2 trials and a detailed management plan was instituted in phase 3 trials such that rash leading to permanent discontinuation of all study drugs decreased from 5.2% in phase 2 to 0.8% in phase 3. Mechanisms of rash were investigated, such as metabolite characterization, HLA analysis and exposure-response relationships, but no mechanism was identified. Most cases of rash were mild-to-moderate and occurred earlier on the telaprevir arms compared to SOC; the timing of rash on telaprevir is during the first 4 weeks of treatment. Severe rash other than Stevens-Johnson Syndrome (SJS) occurred in 4% of subjects who received telaprevir compared to less than 1% who received SOC. A Dermatology Expert Panel was convened by the applicant; cases were reviewed retrospectively and adjudicated. In addition DAVP consulted the Division of Dermatology and Dental products.

Severe cutaneous adverse reactions such as SJS were reported in less than one percent of subjects treated with telaprevir compared to none on control arms. Specifically, three cases of SJS were reported in the data base; all were on the telaprevir-containing arms. One case was definite, but occurred 11 weeks after discontinuation of telaprevir while the subject was on pegylated interferon and ribavirin making it unlikely that it was related to telaprevir exposure. There were two other cases, one probable and one possible. There were 11 cases of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS); one was definite, 2 were probable and 8 were possible. Organ involvement was absent in 9 and unconfirmed in 2 cases. There were no cases of toxic epidermal necrolysis (TEN). No deaths were related to serious skin reactions.

The pegylated interferon labels list SJS in the warnings and precautions section of the label cross-referenced to the post-marketing section as does the ribavirin label; the ribavirin label also lists TEN. Dr. Brenda Carr, consulting FDA dermatologist notes in her review that suspected severe cutaneous adverse reactions are rare and clinical trial sample sizes are generally not large enough to detect these rare events. She further notes

that most of these events were suspected on a case review by an expert panel and not by investigators. The implication is that events such as SJS may have been under reported in pegylated interferon and ribavirin development programs. The Antiviral Drugs Advisory Committee dermatology consultant, Dr. Bigby also stated his concerns about severe cutaneous adverse reactions in the clinical trials and cautioned that more will be seen post-approval. He also thought, however that the benefits of telaprevir outweighed the risks by voting for approval and agreeing that the Applicant needs to develop educational materials for health care providers and patients.

Serious skin reactions /rash will be listed in the warnings and precautions section of the telaprevir label. In addition to describing these events, the following management plan is outlined:

If a severe cutaneous adverse reaction such occurs as SJS, telaprevir combination treatment must be discontinued immediately and not restarted. Patients should be monitored until the rash has resolved.

Patients with mild or moderate rashes should be followed for progression of rash and development of systemic symptoms. Sequential discontinuation of the telaprevir combination may be necessary beginning with telaprevir. Any rash associated with fever, lymphadenopathy, facial edema, or other significant systemic or constitutional symptoms, mucous membrane ulceration, target lesions, epidermal detachment, vesicles or bullae constitutes a serious skin reaction and requires immediate and permanent discontinuation of telaprevir, peginterferon alfa and ribavirin and prompt referral for medical care.

Patients will be referred to the prescribing information for peginterferon alfa and ribavirin for serious skin reactions. Treatment of rash with oral antihistamines and topical or systemic steroids may provide symptomatic relief but effectiveness of these measures has not been established. In patients requiring treatment with a systemic corticosteroid, telaprevir should be discontinued.

ANEMIA

Non-clinical studies identified hematologic effects as a target for monitoring in clinical trials. In addition, pegylated interferon and ribavirin are known to have hematologic effects. The primary toxicity of ribavirin is hemolytic anemia that has been associated with fatal and non-fatal myocardial infarctions. Pegylated interferon suppresses bone marrow function resulting in potentially severe cytopenias and associated infectious complications. Ribavirin may also potentiate neutropenia and lymphopenia caused by interferon.

Telaprevir given with pegylated and ribavirin increases rates of anemia. The mechanism is thought to be related to hemolytic anemia and decreased red blood cell production. Exposure-response analyses bear this out as well. Higher telaprevir exposure was significantly associated with anemia risk defined as hemoglobin less than 10 g/dL or any decrease from baseline greater than 3.5 g/dL. See Pharmacometrics review.

The timing of anemia is such that the nadir is reached between weeks 12-14. Once telaprevir therapy has been completed at the end of week 12, hemoglobin levels rise to levels seen with pegylated interferon and ribavirin and approach baseline values by follow-up week 24.

More subjects receiving telaprevir compared to SOC in phase 3 trials experienced anemia to levels between 8.5 and 10 g/dL, 27% versus 12%. Adverse events leading to permanent discontinuation of telaprevir were 4.2% on the telaprevir arms compared to less than 1% on SOC. Similarly, there were more adverse events leading to ribavirin dose reductions on telaprevir containing arms compared to SOC, 23% versus 10% and more blood transfusions in subjects who received telaprevir as compared to SOC, 6% versus 1%. ESAs are not labeled for this indication and were not permitted in the clinical trials except for sites in France and were used in less than one percent across treatment groups.

Severe anemia will also be described in the warnings and precautions section of the label. Monitoring of hemoglobin will be recommended as well as a management plan.

9. **Mortality:** In the clinical review**,** it was stated that narratives were reviewed for the 11 deaths in the data base, 7 on telaprevir and 4 in the control group. One additional death was submitted in the safety update and occurred in a subject randomized to receive telaprevir. Adverse events leading to death fell into a few categories: infections, malignant neoplasms, nervous system disorders, cardiovascular events, trauma and respiratory failure. Six of the seven deaths in telaprevir subjects in the original NDA data base occurred more than 100 days after the last dose of telaprevir. These events were unlikely related to telaprevir. The additional death in the safety update occurred 42 days after the last dose of telaprevir in a 69 year old male with a history of hypertension who suffered a myocardial infarction.

10. **Risk Minimization Considerations:** DAVP and DRISK within OSE decided that a REMS was not required for telaprevir. A Medication Guide will be part of labeling for telaprevir. Labeling will contain warnings and precautions related to pregnancy exposure, anemia and serious skin reactions. Since there were no deaths related to telaprevir-associated

rash, there will not be a boxed warning in the label. A safety meeting was held with OSE to discuss monitoring of post-marketing events.

Post-marketing requirements (PMRs) and commitments (PMCs) center on submission of data from proposed pediatric studies based on PREA, adult clinical studies in special populations, clinical virology studies, and pharmacogenomics studies. Specifically, the following draft PMRs/PMCs and timelines have been requested:

PREA PMRs

1. Conduct a single-dose pharmacokinetics study (or substudy) 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.

Protocol Submission: September, 2011
Study Completion: June, 2014
Study Report Submission: October, 2014

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, determination of durability of response, and characterization of telaprevir resistance-associated substitutions.

Protocol Submission: (b) (4)
Study Completion: (b) (4)
Study Report Submission (without long-term follow-up): (b) (4)
Study Report Submission of Long-Term Safety Follow-Up: (b) (4)

Clinical PMCs

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

Protocol Submission: September, 2011
Study Completion Date: (b) (4)
Study Report Submission: (b) (4)

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

Protocol Submission: September, 2011
Study Completion Date: (b) (4)
Study Report Submission: (b) (4)

5. Conduct a trial (VX11-950-115) to evaluate safety and treatment responses among treatment naïve and experienced HIV/HCV co-infected subjects (b) (4).

Protocol Submission: January, 2012
Study Completion date: June, 2014
Study Report submission: December, 2014

Pharmacogenomics PMCs
6. Conduct a genome-wide association study (GWAS) to identify factor(s) associated with severe skin reactions to telaprevir/peginterferon/ribavirin using cases from existing DNA sub-studies and appropriately selected controls.

Protocol Submission: October, 2011
Study Completion: (b) (4)
Study Report Submission: (b) (4)

Clinical Virology PMRs
7. 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)

8. 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.

Clinical Pharmacology PMR
9. Conduct a PK study 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 HCV patients on HD.

Protocol Submission: to be proposed by Vertex
Study Completion: to be proposed by Vertex
Study Report Submission: to be proposed by Vertex

11. Advisory Committee
An advisory committee was held on April 28, 2011. The following questions were posed to the advisory committee; responses are paraphrased.

1. Rash associated with telaprevir use was common and sometimes severe and treatment-limiting and anemia was more frequent and more severe in patients treated with telaprevir. Please comment on the safety profile of telaprevir, focusing on the increased frequency and severity of rash and anemia when telaprevir is added to pegylated interferon and ribavirin. Do these adverse events affect your risk/benefit assessment and, if so, how?

The overwhelming consensus of the committee was that the risks did not outweigh the benefits for telaprevir. Several committee members noted that rash associated with antiretroviral agents such as abacavir and nevirapine, is fairly common, but adequately managed due to proper identification. The committee agreed that there must be strong and detailed educational materials for both patients and healthcare providers to help identify and manage these adverse events.

2. Considering the overall risks and benefits, do the available data support approval of telaprevir for treatment of treatment-naive and treatment-experienced patients with chronic hepatitis C genotype 1 in combination with pegylated interferon and ribavirin?

VOTE: Yes/No/Abstain

a) *If no, what additional studies are recommended?*
b) *If yes, proceed with the remaining questions.*

Following discussion, the Committee voted unanimously, 18-0 to approve telaprevir.

3. Please comment on the strength of evidence to support response-guided therapy with telaprevir in combination with pegylated interferon and ribavirin for the following patient groups?

a) Treatment-naïve

b) *Prior relapsers*

Overall, the Committee was in support of RGT for treatment naïve subjects based on Trials 108 and 111. Regarding RGT in relapsers, most committee members supported the concept based on phase 2 trials and comparable interferon sensitivity to naives.

4. Please comment on the strength of evidence to support a recommendation for use in specific populations, including but not limited to Blacks/African Americans and patients with cirrhosis. What, if any, additional efficacy or safety data are needed for specific populations?

Although representation was limited, Blacks/African Americans achieved SVR rates on a telaprevir-containing regimen that were also approximately 30% above that seen with SOC, but lower than Caucasians. It was mentioned that there is a need for additional information in patients who are over 65 years of age and in null responders with cirrhosis.

5.Are there any other post marketing studies you would like to see conducted to further define risks or optimal use of telaprevir?

Resistance and cross-resistance concerns were discussed in detail. In addition, the committee also had concerns regarding how health care providers and patients will be asked to manage anemia and rash. More studies of under - represented populations such as Blacks/African Americans, patients with cirrhosis and those with bleeding disorders were also suggested. The committee also mentioned the need to conduct drug-drug interaction studies of telaprevir with other HIV drugs, other oral contraceptives and to explore the interaction of IL28B with outcomes. The committee mentioned examining twice daily dosing to improve adherence; this concept is already being explored by Vertex.

Conclusions and Recommendations:

Chronic hepatitis C is a serious and life-threatening disease affecting up to 4 million patients in the United States. Though the incidence is decreasing, the risk of complications including death will continue without the use of more potent therapies. Telaprevir is a potent, direct-acting antiviral belonging to the NS3-4A protease inhibitor class and, when added to pegylated interferon and ribavirin led to SVR rates at least 30 % above that seen with SOC, even in difficult-to-treat populations. In subjects with favorable viral kinetics and interferon sensitivity, SVR rates greater than 90% were seen in some populations.

Serious adverse events included anemia at rates beyond those seen with SOC. Anemia can be monitored and managed by dose reducing ribavirin or discontinuing the regimen. Rash could be severe, but rarely. Cases of severe cutaneous adverse reactions such as SJS were seen in the NDA data base which is concerning. Even with a rash management plan it is anticipated that more SJS cases will be seen post-marketing.

In sum, based on the data submitted in the NDA, I am in full agreement with the multidisciplinary review team that telaprevir should be approved in adult patients with genotype 1 CHC. The totality of the data supports the conclusion that the benefits of a telaprevir-containing regimen outweigh the risks in the setting of toxicity management plans and educational campaigns developed by the Applicant.

Labeling, post-marketing requirements and post-marketing commitments, address the concerns of the review team, consultants and the advisory committee.

This is truly an exciting time for patients with CHC. As more patients achieve SVR it is anticipated that rates of cirrhosis, hepatocellular carcinoma, liver transplantation and mortality will decline. Similar to the positive outcomes seen with potent antiretroviral combinations that were approved for HIV in the 1990’s, with the approval of direct-acting antivirals such as telaprevir we are beginning a new era for patients with hepatitis C.

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/s/

DEBRA B BIRNKRANT
05/13/2011