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RESEARCH**

APPLICATION NUMBER:

205123Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

New Molecular Entity Risk Management Review

Date: October 7, 2013; *Revised October 21, 2013*

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

Team Leader: Kendra Worthy, Pharm. D., DRISK

Division Director: Claudia Manzo, Pharm. D., DRISK

Drug Name: TBD, TMC435 (simeprevir) Oral Capsule

Therapeutic Class: Protease Inhibitor for Hepatitis C Virus

Dosage and Form: 150 mg capsule taken once daily, oral route, with food

Indication(s): For the treatment of chronic Hepatitis C Virus genotype-1 infection, in combination with peg-interferon alfa and ribavirin in adult patients with compensate liver disease (including cirrhosis).

Application Type/Number: NDA 205-123/Supplement 00/Sequence 01

PDUFA Deadline: November 28, 2013, *Revised as November 22, 2013*

Applicant: Janssen Research and Development, LLC. (Janssen)

OSE RCM #: 2013-848

TSI: Not Applicable

1 INTRODUCTION

This Division of Risk Management (DRISK) review provides evaluation of whether a risk evaluation and mitigation strategy (REMS) is needed for the proposed new molecular entity (NME), TMC435 (Simeprevir).¹ Janssen proposes use of simeprevir for the treatment of chronic HCV (CHC) genotype-1 (GT-1) infection, in combination with peg-interferon-alfa (PegIFN α) and ribavirin (RBV), in adult patients with compensated liver disease (including cirrhosis). This New Drug Application (NDA) 205-123, received on March 28, 2013/ Supplement (Suppl.) 00/Sequence (Seq.) 01, was submitted to the Division of Antiviral Drugs (DAVP). The applicant did not submit a proposed REMS for TMC435 in this NDA.

Under the Prescription Drug User Fee Act (PDUFA) V, the Agency is required to perform a benefit-risk assessment of all NMEs submitted as an original NDA or biologic license application (BLA) which includes the documented evaluation of the need for a REMS.

2 BACKGROUND

TMC435, Simeprevir, is a specific inhibitor of the hepatitis C virus (HCV) NS3/4A protease-dependent cleavage of the HCV poly-protein that inhibits viral replication in infected host cells. The applicant claims that the clinical data in the TMC435 clinical development program demonstrates that the proposed TMC435, 150 mg oral capsule, a once daily (qd) regimen, in combination with Peg-IFN α and RBV, addresses current unmet medical needs and offers a meaningful improvement to the approved therapies for the treatment of CHC infection.² Based on the applicant's perspective³, the unmet medical need for new HCV treatments include:

- increased sustained virologic response (SVR) rates
- demonstrated efficacy and safety in HCV patients
- improved safety and tolerability profiles
- low drug-drug interaction (DDI) potential
- increased proportion of patients eligible for shorter treatment duration
- reduced pill burden and simplified treatment, e. g., by providing once-daily regimens, which will facilitate patient adherence

HCV Infection

According to the applicant, the HCV is one of the most important causes of liver-related morbidity and mortality world-wide. An estimated 130 to 210 million people (3% of the

¹ The applicant's proposed proprietary name is SOVRIAD; however, SOVRIAD is an approved Trade Name in the United Kingdom (UK) and it is similar to the name [REDACTED] ^{(b) (4)}. The second-choice proposed proprietary name is OLYSIO. The internal action on the proposed proprietary name is pending.

² NDA 205-123 Simeprevir (TMC435) in Global Submit, Module 1.2 Request for Priority Review, p 4/10

³ See the original NDA 205-123, TMC435 submission, TOC, Module 2.0, Section on Clinical Overview

global population) are currently infected, with 2 to 4 million newly infected annually.⁴ Between 70% and 90% of acute infections become chronic and may lead to liver fibrosis, cirrhosis, liver failure, hepatocellular carcinoma, death or require a liver transplant. The CHC infection has become a major health care burden globally and in the United States (US).⁵

HCV has been classified into at least 6 major genotypes (designated 1 – 6) and many subtypes (a, b, c, etc.) Genotypes 1 to 3 have a world-wide distribution, with genotypes 1a and 1b being the most common and accounting for 60% of global HCV infections, mainly in North America, Europe, and Japan.⁴ Genotype 1a is predominantly present in North America and northern Europe, while Genotype 1b is predominantly found in southern and Eastern Europe and Japan.⁶

The CHC infection is found in about 30% of human immunodeficiency virus (HIV) positive (+) persons. The presence of HIV infection has been shown to accelerate the natural history of HCV infection in terms of the progression to cirrhosis and end-stage liver disease.⁷

Priority Review Designation

Before 2011, the standard of care treatment of HCV infection for all HCV genotypes was the combination of PegIFN α and RBV for 48 weeks. In addition to the poor treatment response in HCV genotypes 1 or 4 infected patients or certain subpopulations (e.g., patients with advanced fibrosis, non-responders to prior PegIFN α /RBV therapy), this treatment has been associated with considerable side effects and is therefore burdensome for patients. The major side effects include hematologic abnormalities, fatigue, influenza-like symptoms, gastrointestinal disturbances, and neuropsychiatric symptoms. These side-effects may be treatment-limiting, often require dose reduction, drug discontinuation, or adjunctive treatment with erythropoietin stimulating agents in the case of anemia.⁸

Approved Products for the Treatment of Chronic HCV Infection

- **Telaprevir (INCIVEK):** (NDA 201-917) Approved on May 23, 2011 as a NME, Film-Coated Tablet, in combination with PegIFN α /RBV, for the treatment of genotype 1 chronic hepatitis C (CHC) in adult patients with compensated liver disease. The dosage and administration is 750 mg taken 3 times a day by mouth (7 to 9 hours apart) with food (not low fat).

⁴ European Association for the Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis virus infection. *J Hepatol.* 2011; 55(2):245-264.

⁵ World Health Organization. Hepatitis C. Available at: <http://www.int/csr/disease/hepatitis/whocdscriyo2003/en/index2.html>, accessed 05Mar2013

⁶ Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the speed of hepatitis C virus in Egypt. *Lancet* 2000; 355 (9207):887-891.

⁷ Kontorinis N, Agrawal K, and Dieterich DT. Treatment of hepatitis C virus in HIV patients: a review. *AIDS.* 2005;19(suppl. 3):S166-S173.

⁸ Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology.* 2002; 36:S237-S244.

- CLINICAL SAFETY (from approved labeling dated April 25, 2013)
 - BOX WARNING – WARNING: SERIOUS SKIN REACTIONS, Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with INCIVEK combination treatment.
 - CONTRAINDICATIONS
 - All contraindications to PegIFN α and RBV also apply since INCIVEK must be administered with PegIFN α and RBV. Co-administration with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
 - WARNINGS AND PRECAUTIONS –
 - Serious Skin Reactions/Rash: Fatal and non-fatal serious skin reactions (including SJS, DRESS, and TEN) have been reported. Patients with mild to moderate rash should be monitored for progression. If the rash progresses and becomes severe, INCIVEK, should be discontinued.
 - Anemia: Monitor hemoglobin prior to and at regular intervals during INCIVEK combination treatment.
 - Pregnancy: Use with Ribavirin and PegIFN α : RBV may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy; use at least 2 effective methods of contraception, and undergo monthly pregnancy tests.
 - PATIENT COUNSELING INFORMATION - See FDA-approved Patient Labeling (Medication Guide)
 - Serious Skin Reactions/Rash
 - Pregnancy
 - Hepatitis C virus Transmission
 - Importance of Hydration
 - Administration

Post marketing risk management for telaprevir is via routine pharmacovigilance. The Agency did not require a REMS for approval of INCIVEK.

- **Boceprevir (VICTRELIS):** (NDA 202-258) Approved on May 13, 2011 as a NME, Oral Capsule, a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of CHC genotype 1 infection, in combination with PegIFN α and RBV, in adult patients (18 years of age or older) with compensated liver disease. The dosage and administration is 800 mg administered orally three times daily (every 7 to 9 hours) with food (a meal or light snack).

- CLINICAL SAFETY (from approved labeling dated September 18, 2013)
 - o There is not a BOXED WARNING in labeling
 - o CONTRAINDICATIONS
 - All contraindications to PegIFN α and RBV also apply since VICTRELIS must be administered with PegIFN α and RBV. Because RBV may cause birth defects and fetal death, boceprevir in combination with PegIFN α and RBV is contraindicated in pregnant women and in men whose female partners are pregnant. Contraindicated in patients with a history of hypersensitivity reaction to Boceprevir.
 - o WARNINGS AND PRECAUTIONS: Use of VICTRELIS with RBV and PegIFN α :
 - RBV may cause birth defects and fetal death. Avoid pregnancy in female patients and female partners of male patients.
 - Anemia - The addition of VICTRELIS to PegIFN α and RBV is associated with an additional decrease in hemoglobin concentrations compared with PegIFN α and RBV alone.
 - Neutropenia - Addition of VICTRELIS to PegIFN α and RBV may result in worsening neutropenia associated with PegIFN α and RBV alone.
 - Hypersensitivity - Serious acute hypersensitivity reactions (e.g., urticaria, angioedema) have been observed during combination therapy with VICTRELIS, PegIFN α , and RBV.
 - o PATIENT COUNSELING INFORMATION - See FDA-approved patient labeling (Medication Guide)
 - Pregnancy
 - Anemia
 - Neutropenia
 - Hypersensitivity
 - Missed VICTRELIS doses
 - Hepatitis C virus Transmission

Post marketing risk management for boceprevir is via routine pharmacovigilance. The Agency did not require a REMS for approval of VITRELIS.

Approved Anti-Viral Product with Worse Serious Skin Risks

- **Darunavir ethanolate (PREZISTA)** Oral Suspension and Tablet Form was originally approved June 2006 as a HIV-1 protease inhibitor indicated for the treatment of HIV-1 infection in adults. The approved labeling includes WARNINGS AND PRECAUTIONS with Severe Skin Reactions (inserted on June 2012). Serious risks of skin reactions with exposure to PREZISTA range from mild to severe, including Stevens Johnson Syndrome, toxic epidermal necrolysis and acute

generalized exanthematosus pustulosis. There is no Medication Guide or REMS for PREZISTA. The INSTRUCTIONS FOR USE are included in the product packaging received by the patient.

Armamentarium for Therapy for HCV Infection

See the **Discussion** section of this review for brief comments about HCV treatment duration in the context of the two cited approved products and the risks associated with these therapies in HCV infection.

Generic Products for the Treatment of Chronic HCV

The Agency is not aware of any Abbreviated NDA (ANDA) submissions to the FDA and are not aware of any patent challenges (though a patent challenge may occur at any time).

2.1 Regulatory History

The regulatory history specific to this NME application, TMC435, follows:

June 21, 2011: The Agency granted the applicant Fast Track designation

February 3, 2012: The Agency recertified the Fast Track designation

January 30, 2013: Pre-NDA Meeting was held for the Investigational New Drug Application IND 075-391 (TMC435). A preliminary discussion on the need for a REMS program was not held during this meeting. The DAVP agreed with the applicant's proposal to include a Patient Package Insert in the TMC435 NDA and as part of TMC435 labeling.

March 28, 2013: The applicant submitted the original NDA 205-123 for TMC435 (simeprevir) in CHC and requested a Priority Review Designation

April 12, 2013: The applicant submitted request for the Proprietary Name, SOVRIAD

May 7, 2013: The applicant was granted Priority Review designation

July 26, 2013: The applicant submitted a 2-Month Safety Update Report (SUR). The DAVP requested an early 2-Month SUR during the Pre-NDA Meeting (rather than the usual 4-Month SUR) due to the Priority Review designation for this NDA.

September 10, 2013: The applicant submitted labeling revisions based on comments from the DAVP (dated August 28 and September 5, 2013).

Pending - October 24, 2013: An Antiviral Drugs Advisory Committee meeting is scheduled to be held to discuss the efficacy and safety of TMC435 in CHC.

2.2 Materials Reviewed

March 28, 2013: Original NDA 205-123 TMC435 (simeprevir) proposed for the treatment of CHC

August 26, 2013: Medical Officer Clinical Review of Priority NDA 205-123 Simeprevir (TMC435)

September 26, 2013: FDA Anti-Viral Products Advisory Committee Background Package for NDA 205-123

October 3, 2013: The DAVP's substantially complete proposed labeling for TMC435

3 Overview of the Clinical Development Program

The clinical development program for TMC435 (simeprevir) consisted of three (3) pivotal Phase 3 clinical trials, (TMC435-TiDP16-C208, TMC435-TiDP16-C216, and TMC435-HPC3007), referred to in this review as C208, C216, and HP3007. These three trials support 60-weeks of efficacy and safety data.⁹

The trials assessed the combination of simeprevir (150 mg daily for 12 weeks) plus PegIFN/RBV abbreviated as PR, alone for either 12 or 36 weeks, based on an individual patient's virologic response to therapy (response-guided therapy abbreviated as RGT). The control arm in each of these trials was placebo (PBO) for 12 weeks, in combination with PR for a fixed, 48-week duration. Trials C208 and C216 were almost identical in design and enrolled only treatment-naïve patients.

Efficacy

The primary efficacy endpoint for the Phase 3 trials was sustained virologic response (SVR) 12 weeks after the planned end-of-treatment (SVR12). The SVR12 was defined as an undetectable HCV RNA at the end-of-treatment and HCV RNA < 25 IU/mL at 12 weeks after the planned, end-of-treatment. Stratification factors included a HCV genotype/ subtype.

- The efficacy of TMC435 in combination with PR was superior to PBO in combination with PR in patients with HCV genotype 1, both in treatment-naïve and treatment-experienced populations.
- Differences in SVR rates between the TMC435/PR and PBO/PR treatments in the Phase 3 studies were statistically significant (p<0.001) and clinically relevant in treatment-naïve patients and prior relapsers, with treatment differences of 30% and 42%, respectively.
- As trials C208 and C216 were performed in a HCV treatment-naïve population and employed almost identical study designs; the efficacy results were pooled for analyses. The pooled SVR12 results from the treatment-naïve studies demonstrated an SVR12 rate of 80% in the simeprevir treatment group and 50% in the control group.
- In the HPC3007, the SVR12 rate in the simeprevir group was 79% compared with 36% in the control group. See the **Appendix**, to this review, **Table 1**, Efficacy Results presented in the FDA Advisory Committee Background Package for NDA 205-123, TMC435.

3.1 Clinical Safety

⁹ The information in **Section 3**, Overview of the Clinical Development Program, in this review, is from three sources: NDA 205-123 application in Global Submit (received on March 28, 2013), FDA Advisory Committee Background Package (dated September 26, 2013), and the Medical Officer Clinical Review (dated August 26, 2013).

The safety profile of TMC435, in combination with PR, in patients with HCV genotype 1 infection, who were treatment-naïve or who had previously relapsed following interferon therapy with or without RBV, was based on pooled data from three Phase 3 trials.

Exposure

The primary safety data included a total of 1178 patients who received simeprevir or PBO in combination with PegIFN and RBV. Of the 1178 patients, 781 patients were randomized to receive simeprevir 150 mg once daily for 12 weeks and 397 patients were randomized to receive PBO once daily for 12 weeks.

Deaths

Four deaths were reported in patients receiving simeprevir in the pooled Phase 2b and Phase 3 analysis (including study C205, C206, C208, C216, and HPC3007). The reported causes of death included: 1) bacterial meningitis and brain hemorrhage; 2) colon cancer; 3) presumed cardiopulmonary event; 4) bilateral pneumonia and septic shock. No deaths were reported in the control arms. In each of these cases, the patient's death was judged as causally unrelated to simeprevir by the applicant and the DAVP concurred.

Serious Risks with Simeprevir/PegIFN /RBV Combination Treatment

The draft substantially complete proposed labeling (SCPL) does not include a BOXED WARNING. The WARNINGS AND PRECAUTIONS (Section 5) includes the following events:



¹⁰ The Agency has not made a final decision on the proposed Trade Name, SOVRIAD. The applicant submitted two other proposed proprietary names that are currently under Agency review.

Adverse Reactions and the Clinical Studies

The most common adverse reactions (greater than 20% of patients) in patients receiving the combination of simeprevir with PegIFN and RBV were: rash (including photosensitivity), pruritus and nausea (labeling Section 6.1). In the Phase 3 trials, rash (photosensitivity reactions) was observed in 28% of simeprevir-treated patients compared to 20% of patients treated with PBO during the 12 weeks of treatment with simeprevir/PBO in combination with PegIFN/RBV. There were 56% of rash events in the simeprevir group occurred during the first 4 weeks of treatment with simeprevir, with 42% of cases occurring in the first 2 weeks. Most of the rash events in simeprevir-treated patients were of mild or moderate severity (Grade 1 or 2). Severe (Grade 3) rash occurred in 1% of simeprevir-treated patients, compared to less than 1% of patients treated with PBO with PegIFN/RBV.

- Rash and Photosensitivity

In these clinical trials, adverse reactions under the specific category of photosensitivity were reported in 5% of simeprevir-treated patients compared to 1% in patients treated with PBO during the 12-weeks of treatment with simeprevir/PBO in combination with PegIFN and RBV. Most photosensitivity reactions in simeprevir-treated patients were of mild or moderate severity (Grade 1 or 2). There were 2 simeprevir-treated patients who experienced photosensitivity reactions which resulted in hospitalization. No life-threatening photosensitivity reactions were reported.

- Dyspnea

During the 12 weeks of simeprevir-treatment, dyspnea was reported in 12% of simeprevir-treated patients compared to 8% with PBO, PegIFN and RBV (all grades; pooled Phase 3 trials). All dyspnea events reported in simeprevir-treated patients were of mild or moderate severity (Grade 1 or 2). There were no Grade 3 or 4 dyspnea events reported and no patients discontinued treatment with simeprevir due to dyspnea; 61% of dyspnea events occurred during the first four weeks of treatment with simeprevir.

- Laboratory Abnormalities

There were no differences between treatment groups for the following laboratory parameters: hemoglobin, neutrophils, platelets, aspartate aminotransferase, alanine aminotransferase, amylase, or serum creatinine. There was a trend with higher treatment-emergent laboratory abnormalities in simeprevir-treated patients than in patients treated with PBO (e. g., alkaline phosphatase, hyperbilirubinemia).

Substantially Complete Proposed Simeprevir Labeling

The SCPL, Section 17. Patient Counseling Information includes Patient Information that focuses on the following risks:

- Pregnancy
- Photosensitivity
- Administration
- Hepatitis C Virus Transmission

3.2 Discussion

The armamentarium of therapies for HCV infection includes two new direct-acting anti-viral agents (DAAs), telaprevir (Incivek) and boceprevir (Victrelis), administered in combination with PegIFN and RBV, both approved in 2011 for the treatment of CHC genotype 1 infection in adults. The approval of these two drugs changed the treatment standard from dual to triple therapy and shortened the treatment duration from 48 weeks to 24 weeks in patients with HCV genotype 1 infection who are treatment-naïve or relapsed following prior interferon-based treatment.

The co-administration of telaprevir or boceprevir with PegIFN and RBV is associated with increased rates and severity of adverse events (AEs), such as anemia and rash, in comparison to PegIFN and RBV administered alone. The clinical management of the AEs, including red blood cell transfusions and erythropoietin use includes additional risks of treatment. Both telaprevir and boceprevir require three-times daily oral dosing.

Simeprevir, should it be approved, offers the convenience of once daily oral dosing in contrast with the two currently marketed products (Incivek and Victrelis) that require three times per day dosing and administration for the treatment of CHC infection.

The applicant's proposed that the risks observed with simeprevir may be managed with routine post marketing pharmacovigilance and labeling including Patient Information that focuses on the key risks observed with simeprevir, in combination with PegIFN and RBV therapy. The DAVP did not require that the applicant submit a proposed REMS for

At this time, the DRISK and DAVP do not believe that simeprevir is associated with a serious risk(s) that exceeds its' benefit without a REMS program. The rationale follows:

- The DAVP explained that the most likely prescribers for simeprevir will be hepatologists, subspecialists who are familiar with the armamentarium of therapy for HCV, CHC, and HIV-1 infection. Hepatologists understand the known risks and the management with antiviral products with similar and/or worse serious risk profiles compared with simeprevir, particularly, for the risk of severe skin reactions [e.g., darunavir ethanolate (Prezista) and telaprevir (Incivek)].
- The DAVP concluded that the proposed simeprevir labeling with the recommendation to use sunscreen by patients taking simeprevir, is adequate risk mitigation in the Prescribing Information. The DAVP acknowledged that this NDA has limited duration of controlled clinical safety data, 12-weeks.

- The Class of Protease Inhibitors, per se, is most known for the risk of cardiovascular disease in HIV-infected patients.¹¹ However, The DAVP explained that the risk of severe skin reactions associated with use of a specific antiviral product is adequately addressed in the specific product labeling.
- None of the antiviral therapies cited in this review for HCV, CHC, or HIV-1 include a Medication Guide or a REMS program.

There will be an Antiviral Drugs Advisory Committee Meeting on October 24, 2013 to discuss the efficacy and safety of TMC435 (simeprevir). The DRISK will attend this meeting and follow-up with the DAVP during the internal de-briefing discussion.

4 CONCLUSION

The DRISK and the DAVP are in agreement that the benefit risk profile of simeprevir, in combination therapy with PegIFN and RBV, for the treatment of CHC GT-1 infection in adult patients with compensated liver disease (including cirrhosis), is favorable and can be managed with the proposed labeling including Patient Information. The DAVP should consult the DRISK if additional safety information is identified that warrants reevaluation of risk mitigation measures simeprevir.

¹¹ Iloeie UH, Yuan Y, L'italien G, Mauskopf J, Holmberg SD, Moorman AC, Wood KC, Moore RD. Protease Inhibitor exposure and increased risk of cardiovascular disease in HIV-infected patients. *HIV Med* 2005 Jan;6(1):37-44.

APPENDIX

- **Table 1.** Primary Efficacy Results, TMC435 (simeprevir) from Pooled Phase 3 Data*

Table 1: Primary Efficacy Analysis in the Pooled Treatment-Naive Trials (C208 and C216) and Treatment Experienced (Relapser) Trial (HPC3007)

Studies (Number of Subjects)	C208 & C216 (N=785)		HPC3007 (N=393)	
	Pooled TMC435	Pooled PBO	TMC435	PBO
Overall SVR12 ^a	419/521 (80%)	133/264 (50%)	206/260 (79%)	48/133 (36%)
On-treatment failure ^b	43/521 (8%)	88/264 (33%)	8/260 (3%)	38/133 (29%)
Viral Relapse	55/469 (12%)	38/171 (22%)	48/249 (19%)	43/90 (48%)

a. SVR12 is defined as the proportion of subjects with HCV RNA < 25 IU/mL detectable or undetectable 12 weeks after the actual end of treatment.

b. On-treatment failure was defined as the proportion of subjects with detectable HCV RNA at EOT.

* Table 1 is from the FDA Background Package (dated September 26, 2013) for the Antiviral Drugs Advisory Committee

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/s/

CAROLYN L YANCEY

10/21/2013

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CLAUDIA B MANZO

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