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RESEARCH**

APPLICATION NUMBER:

205123Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 205123
Applicant Name	Janssen Research and Development, LLC
Date of Submission	March 28, 2013
PDUFA Goal Date	November 28, 2013
Proprietary Name / Established (USAN) Name	Olysio simeprevir
Dosage Forms / Strength	capsule, 150 mg
Indication	<p>Olysio is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.</p> <ul style="list-style-type: none"> Olysio efficacy has been established in combination with peginterferon alfa and ribavirin, in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis) <p>The following points should be considered when initiating Olysio for treatment of chronic hepatitis C infection:</p> <ul style="list-style-type: none"> Olysio must not be used as monotherapy Olysio efficacy in combination with peginterferon alfa and ribavirin is influenced by baseline host and viral factors Olysio efficacy in combination with peginterferon alfa and ribavirin is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with hepatitis C virus (HCV) genotype 1a without the Q80K polymorphism. Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism. Olysio efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes Olysio or other HCV protease inhibitors
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Adam Sherwat
DMEPA Reviews	Morgan Walker, Carol Holquist, Jamie Wilkins
DMPP & OPDP Reviews	Sharon Mills, Kemi Asante, LaShawn Griffiths, Barbara Fuller
DRISK Review	Carolyn Yancey, Kendra Worthy, Claudia Manzo
DDDP Consult	Brenda Carr, Jill Lindstrom, Susan Walker
Product Quality	Steven Donald, Stephen Langille
Biopharmaceutics Review	Kareen Riviere, Angelica Dorantes, Richard Lostritto
Statistical Review	Yanming Yin, Fraser Smith
Pharmacology Toxicology Reviews	Janice Lansita, Hanan Ghantous, Abigail Jacobs
CMC Review	Celia Cruz, Chunchun Zhang, Kareen Riviere Stephen Miller, Rapti Madurawe,
Clinical Virology	Damon Denning, Eric Donaldson, Jules O'Rear
Clinical Pharmacology Review	Leslie Chinn, Jiang Liu, Jeffrey Kraft, Yuzhuo Pan, Ping Zhao, Jeffry Florian, Mike Pacanowski, Yoriko Harigaya, Yongheng Zhang, Islam Younis
OSI	Antoine El-Hage, Susan Thompson, Kassa Ayalew, Xikui Chen, Sam Haidar, William Taylor
CDTL Review	Mary Singer
Deputy Division Director's Review	Jeff Murray

OND=Office of New Drugs

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

Olysio (simeprevir) is an HCV NS3A/4 protease inhibitor developed for the treatment of chronic hepatitis C genotype 1 infection in combination with other antiviral agents. There are two previously approved HCV NS3A/4 protease inhibitors for hepatitis C genotype 1, Victrelis (boceprevir) and Incivek (telaprevir).

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of simeprevir. For a detailed discussion of NDA 205123, the reader is referred to the individual discipline specific reviews. In addition the Cross-Discipline Team Leader Review and the Deputy Division Director Review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

The Office of New Drug Quality Assessment finds that the Chemistry, Manufacturing, and Controls (CMC) information in the NDA is adequate to assure the identity, strength, purity, and quality of Olysio (simeprevir) 150 mg capsules. The dissolution method and specification, and the methods validation have been reviewed and found to be acceptable. Stability data currently support a 24-month shelf life for all climactic zones. Natural light can affect the stability of the product; the labeling states that simeprevir capsules should be stored in the original package in order to protect from light. The recommendation from the Office of Compliance regarding the manufacturing facilities is "overall acceptable." The Product

Quality Microbiology Review recommends approval. The application is recommended for approval from the standpoint of CMC.

The recommendation from the pharmacology/toxicology reviewers is for approval. The target organs identified in the nonclinical studies included the gastrointestinal tract and the liver. At high doses 28-times the human exposure based upon AUC, the heart was identified as a potential target organ with acute endocardial and myocardial necrosis. The labeling categorizes simeprevir use with ribavirin and peginterferon as pregnancy category X because of reproductive toxicity of ribavirin (birth defects and/or fetal deaths) and peginterferon alfa (an abortifacient). The product labeling describes in the Warnings and Precautions section the risk of embryo-fetal toxicity, that a pregnancy test with a negative result should be obtained before initiating therapy, that 2 effective contraceptive methods must be used during treatment and for 6 months after completing treatment and pregnancy tests should be monitored during this time period. The labeling also provides information on the ribavirin pregnancy registry.

The Clinical Virology Reviewer recommends that the data in NDA 205123 support approval. The Clinical Virology Review notes the observed lower SVR rates in patients with the genotype 1a NS3 Q80K polymorphism at baseline and that simeprevir treated patients that failed to achieve SVR with Q80K at baseline frequently developed NS3 R155K virus which is expected to be cross-resistant to other NS3/4A inhibitors, including boceprevir and telaprevir. Hence, the product labeling strongly recommends that patients with genotype 1a be screened for the NS3 Q80K polymorphism and if present, that alternative therapy should be considered. The labeling also describes mutations associated with reduced susceptibility to simeprevir. Treatment emergent resistance associated mutations were also identified utilizing next generation nucleotide sequencing data. The analyses identified previously described resistance mutations and two additional low frequency mutations.

The Clinical Pharmacology reviewers find the data in the application are acceptable and recommend approval for the application. Simeprevir is orally bioavailable with the majority of the dose absorbed and 31% of the dose excreted as unchanged drug in the feces based upon a mass balance study. Simeprevir is highly protein bound in plasma and is predominantly as unchanged simeprevir in the plasma. The metabolite M21 was identified in plasma and represents 8% of the simeprevir AUC. The primary route of simeprevir elimination is hepatobiliary excretion. No dosage adjustment is required in patients with mild hepatic impairment. No dose adjustment for simeprevir can be recommended based upon the currently available data for patients with moderate or severe hepatic impairment. CYP3A is the primary enzyme involved in the biotransformation of simeprevir. Co-administration of simeprevir with substances that are moderate or strong inducers or inhibitors of cytochrome P450 3A (CYP3A) is not recommended because this may lead to significantly lower or higher exposure of simeprevir, respectively.

Clinical Trials of simeprevir were performed in treatment-naïve patients, in patients who relapsed after prior interferon based therapy, and in patients who failed prior therapy with peginterferon and ribavirin (PR). In the phase 3 trials, patients received simeprevir plus PR or PR alone. For patients in each of the trials that received simeprevir + PR, SVR12 rates were higher compared to patients that received PR. Based upon the results of these trials, the

labeling provides dosing instructions for treatment naïve and prior relapse patients of 12 weeks of simeprevir + PR followed by an additional 12 weeks of PR. For prior non-responder patients, 12 weeks of simeprevir +PR is followed by an additional 36 weeks of PR. The labeling notes the reduction in efficacy in the presence of the NS3 Q80K polymorphism at baseline for genotype 1a patients, strongly recommends screening, and if the polymorphism is present that alternative therapy should be considered. The results of the trial support the efficacy of simeprevir for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. The labeling describes the populations studied and provides dosing recommendations for treatment regimens and treatment stopping rules for patients with inadequate response on therapy.

The safety database included 1,153 HCV-infected subjects that received simeprevir 150mg po QD for 12 weeks. The most common side effects reported in clinical trials for participants treated with simeprevir in combination with peginterferon-alfa and ribavirin were rash (including photosensitivity), itching (pruritis) and nausea. Serious photosensitivity reactions resulting in hospitalization were reported.

The product labeling includes statements in the Warnings and Precautions section on photosensitivity reactions and a separate statement on rash. The photosensitivity warning statement recommends limiting sun exposure and using sun protective measures. Simeprevir is to be used with ribavirin and peginterferon alfa; therefore the label includes a Warnings and Precautions statement on embryo-fetal toxicity noting that ribavirin may cause birth defects or death of the exposed fetus and that peginterferon is an abortifacient. The labeling also includes Warnings and Precautions statements on sulfa allergy, that simeprevir must not be used as monotherapy and should be used in combination with peginterferon alfa and ribavirin, and a statement on drug interactions with CYP3A inducers or inhibitors. In addition, a patient package insert for simeprevir is also included. A postmarketing requirement to conduct a trial in chronic hepatitis C patients conducted in the Asia-Pacific region will provide additional information on observed increased exposures in this patient population and rates of adverse effects.

NDA 205123 was presented before the Antiviral Drugs Advisory Committee. On the question of whether the available data support the approval of simeprevir for treatment of HCV genotype 1 infection in combination with pegylated interferon and ribavirin the committee voted 19 Yes; 0 No; 0 Abstain. The committee also provided advice on the issues of rash, photosensitivity reactions, and reduced efficacy in the setting of a baseline NS3Q80K polymorphism. The committee also recommended that more data are needed in a number of patient populations including African Americans, Hispanics, Asians, prior PR nonresponders (null and partial responders), cirrhotic patients, HIV/HCV-coinfected patients, pediatric patients, and patients with co-morbidities (including chronic renal failure). Some committee members also noted that pegylated interferon and ribavirin based regimens are not likely to be preferred treatment options in the future.

We are waiving the pediatric study requirement for ages less than 3 years because necessary studies are impossible or highly impractical. Chronic hepatitis C infection is relatively benign

in this age group; spontaneous clearance is possible and the risk-benefit balance would not favor treatment in this age group.

We are deferring submission of a pediatric study for ages 3 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

In summary, I agree with the review team, CDTL, and the Deputy Division Director, that the overall benefits and risks support the approval of NDA 205123 for Olysio (simeprevir) 150 mg capsules as a component of a combination antiviral treatment regimen for the treatment of chronic hepatitis C genotype 1 infection as described in the product labeling. The product labeling adequately describes the safety and efficacy findings. Postmarketing requirements include studies that will provide additional information on resistance mutations and pediatric safety and efficacy data in children ages 3 to less than 18 years of age.

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OND/CDER/FDA

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/s/

EDWARD M COX
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