

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Antiviral Drugs Advisory Committee (AVDAC) Meeting
October 24, 2013**

Location: Sheraton Silver Spring Hotel, Cypress Ballroom
8777 Georgia Avenue, Silver Spring, MD

Issue: The committee discussed New Drug Application (NDA) 205123, simeprevir (a hepatitis C virus protease inhibitor), manufactured by Janssen Pharmaceutical Co., with a proposed indication for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin (two medicines approved to treat chronic hepatitis C) in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin. Compensated liver disease is a stage in which the liver is damaged but maintains ability to function.

These summary minutes for the October 24, 2013 Antiviral Drugs Advisory Committee meeting were approved on December 2, 2013.

I certify that I attended the October 24, 2013 meeting of the Antiviral Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Karen Abraham-Burrell, PharmD
Designated Federal Officer, AVDAC

_____/s/_____
Yoshihiko Murata, MD, PhD
Chairperson, AVDAC

**Summary Minutes of the Antiviral Drugs Advisory Committee Meeting
October 24, 2013**

The following is the final report of the Antiviral Drugs Advisory Committee (AVDAC) meeting held on October 24, 2013. A verbatim transcript will be available in approximately six weeks, sent to the Division of Antiviral Products and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm368547.htm>.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

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The Antiviral Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 24, 2013 at the Sheraton Silver Spring Hotel, Cypress Ballroom, 8777 Georgia Avenue, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and Janssen Pharmaceutical Co. The meeting was called to order by Yoshihiko Murata, MD, PhD (Chairperson); the conflict of interest statement was read into the record by Karen Abraham-Burrell, PharmD (Designated Federal Officer). There were approximately 250 persons in attendance. There were two Open Public Hearing speakers.

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Attendance:

AVDAC Members Present (Voting): Elizabeth Connick, MD; Amanda H. Corbett, PharmD, BCPS, FCCP, CPP; Demetre C. Daskalakis, MD, MPH; Susan S. Ellenberg, PhD; Lawrence S. Friedman, MD; Thomas P. Giordano, MD, MPH; Curt H. Hagedorn, MD; Karen Elizabeth Mark, MD, MPH; Yoshihiko Murata, MD, PhD (Chairperson); Daniel Raymond (Consumer Representative); Russell B. Van Dyke, MD

AVDAC Member Present (Non-Voting): Robin D. Isaacs, MD (Industry Representative)

AVDAC Members Not Present (Voting): Susan S. Ellenberg, PhD; Jeffrey S. Glenn, MD, PhD; Karen Elizabeth Mark, MD, MPH; Doris B. Strader, MD

Temporary Members (Voting): Donald Alcendor, PhD; Michael Bigby, MD; Dean Follmann, PhD; Marc G. Ghany, MD, MHSc; Jonathan Honegger, MD; Louis Y. Korman, MD; Vincent Lo Re, MD, MSCE; Patricia Lupole (Patient Representative)

FDA Participants (Non-Voting): Ed Cox, MD, MPH; Debra Birnkrant, MD; Jeff Murray, MD, MPH; Mary Singer, MD, PhD; Leslie Chinn, PhD; Adam Sherwat, MD

Designated Federal Officer (Non-Voting): Karen Abraham-Burrell, PharmD

Open Public Hearing Speakers: Lynda Dee (AIDS Action Baltimore); Fredrick La Brecque (Caring Ambassadors Program, Inc.)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	Yoshihiko Murata, M.D., Ph.D. Chairperson, AVDAC
Conflict of Interest Statement	Karen Abraham-Burrell, Pharm.D. Designated Federal Officer, AVDAC
FDA Introductory Remarks	Debra Birnkrant, M.D. Director, Division of Antiviral Products (DAVP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	Janssen Pharmaceutical Company
Opening Remarks	Gaston Picchio, Ph.D. Vice President, Hepatitis Disease Area Janssen
Evolving Risks and Benefits of HCV Treatment in the Era of Direct-Acting Antivirals	Nid Afdal, M.D. Chief of Hepatology Beth Israel Deaconess Medical Center
Overview	Katia Boven, M.D. Medical Department Head, Infectious Diseases and Vaccines Janssen
Efficacy	Maria Beumont-Mauviel, M.D. Senior Director, Medical Team Lead SMV Janssen
Virology	Oliver Lenz, Ph.D. Scientific Director, Clinical Virology Lead SMV Janssen
Safety	Wolfgang Jessner, M.D. Medical Director, Trial Physician SMV Janssen

Recommendations for Treatment Management
with Simeprevir and PR

Gaston Picchio, Ph.D.
Vice President, Hepatitis Disease Area
Janssen

Clarifying Questions

BREAK

FDA PRESENTATIONS

Simeprevir - Summary of FDA Review

Adam Sherwat, M.D.
Medical Officer
Division of Antiviral Products (DAVP)
Office of Antimicrobial Products (OAP)
Office of New Drugs (OND), CDER, FDA

Highlights of Simeprevir Clinical Pharmacology

Leslie W. Chinn, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology IV
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Please comment on the safety profile of simeprevir focusing on rash and photosensitivity reactions reported during the clinical trials.
 - a. Does the committee agree that a discussion of the photosensitivity reactions, including a recommendation for sun-protection measures, should be included in the Warnings and Precautions section of the simeprevir prescribing information?

Committee Discussion: *The committee agreed that a discussion of photosensitivity reactions, including recommendations for sun-protection measures, should be included in*

the Warnings and Precautions section of the simeprevir prescribing information. A portion of the discussion centered on whether simeprevir would have to be discontinued for a phototoxic reaction if further sun exposure could be completely avoided. Please see the transcript for details of the committee discussion.

- b. There are apparent differences related to both the clinical presentation and prevention/management strategy for photosensitivity reactions versus rash. Does the committee agree that a separate discussion of rash should be included in the Warnings and Precautions section of the simeprevir prescribing information?

Committee Discussion: *The committee's general consensus was that a discussion of rash should be included in the Warnings and Precautions section of the simeprevir prescribing information. A broad range of opinions was expressed regarding this question. Some committee members suggested that the prescribing information recommend that expert opinion be obtained in the setting of rash. It was noted that there were no reports of severe cutaneous adverse reactions such as SJS, TEN, or DRESS in the clinical trials; however it was also noted that these events are rare and are often not seen during drug development. One committee member noted that there would be no downside to having a warning for rash similar to that included in the telaprevir prescribing information. Some committee members stated it might be confusing to have two separate warnings for photosensitivity and rash; while others stated that it would be better to have two distinct warnings. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Considering the overall risks and benefits, does the available data support approval of simeprevir in combination with pegylated interferon and ribavirin for treatment of HCV genotype 1 infection?

Vote: **Yes= 19** **No = 0** **Abstain = 0**

Committee Discussion: *Considering the overall risks and benefits, the committee unanimously agreed that the available data support approval of simeprevir in combination with pegylated interferon and ribavirin for treatment of HCV genotype 1 infection. The discussion centered on the positive benefit-risk profile of simeprevir and ease of administration in comparison to the currently available HCV protease inhibitors. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** DAVP intends to recommend screening all subjects with GT1a infection for the Q80K viral polymorphism prior to initiation of simeprevir (in combination with pegylated interferon and ribavirin) and that alternative treatment options be considered for patients with this baseline polymorphism. Does the committee agree with DAVP's proposed approach to managing the reduction in efficacy apparent in the setting of the Q80K polymorphism?

Committee Discussion: *The majority of the committee agreed with DAVP's proposed approach to managing the reduction in efficacy apparent in the setting of the Q80K*

polymorphism. Some members stated that alternative treatment options (including an option for no treatment), should be recommended rather than considered for patients with the Q80K polymorphism at baseline. Other committee members noted that because simeprevir/PR treatment is effective in some patients with the Q80K polymorphism at baseline, its use should not be restricted, and that a risk/benefit assessment should be performed on a patient by patient basis. Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** Are there postmarketing studies that should be conducted to further define risks or to optimize use of simeprevir?

***Committee Discussion:** The committee noted that more data is 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). Others thought that additional safety studies to further evaluate rash, photosensitivity, and dyspnea might be important. However, others noted that the HCV treatment paradigm is rapidly changing, and interferon-free regimens may become the standard of care; and thus the patient populations mentioned should be studied with an interferon-free regimen. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:30 p.m.