

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

**Summary Minutes of the Antiviral Drugs Advisory Committee  
April 28, 2011**

*Topic: The committee discussed a new drug application (NDA) 201-917, telaprevir (a hepatitis C virus protease inhibitor), manufactured by VERTEX Pharmaceuticals, Inc., with a proposed indication for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy. Compensated liver disease is a stage in which the liver is damaged but maintains ability to function.*

These summary minutes for the April 28, 2011 Meeting of the Antiviral Drugs Advisory Committee of the Food and Drug Administration were approved on July 27, 2011.

I certify that I attended the April 28, 2011 meeting of the Antiviral Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

\_\_\_\_\_  
**-signed-**  
Paul T. Tran, R.Ph  
Designated Federal Officer, AVDAC

\_\_\_\_\_  
**-signed-**  
Victoria Cargill, M.D., M.S.C.E.  
Committee Acting Chair

**Summary Minutes of the Antiviral Drugs Advisory Committee  
April 28, 2011**

The following is the final report of the Antiviral Drugs Advisory Committee meeting held on April 28, 2011. The verbatim transcript will be available in approximately six weeks, send to the Division of Antiviral Products and posted on the FDA website at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm247236.htm>

All external requests for the meeting transcripts 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 April 28, 2011. The Committee met at the FDA White Oak Campus, 10993 New Hampshire Avenue, Silver Spring, Maryland, the Great Room Conference Center, room 1503. Prior to the meeting, the members and the invited consultants had been provided the background materials from Vertex Pharmaceuticals, Inc. and the FDA. The meeting was called to order by Victoria Cargill, M.D., M.S.C.E. (Committee Acting Chair); the conflict of interest statement was read into the record by Paul Tran, R.Ph (Designated Federal Officer). There were approximately 350 persons in attendance. There were 10 speakers for the Open Public Hearing session.

Issue: The committee discussed a new drug application (NDA) 201-917, telaprevir (a hepatitis C virus protease inhibitor), manufactured by VERTEX Pharmaceuticals, Inc., with a proposed indication for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy. Compensated liver disease is a stage in which the liver is damaged but maintains ability to function.

**Attendance:**

**Antiviral Drugs Advisory Committee Members Present (Voting):**

Victoria Cargill, M.D., M.S.C.E. (Acting Chair), Patrick Clay, Pharm.D., Susan Ellenberg, Ph.D., Barbara McGovern, M.D., Michelle Roland, M.D., Doris Strader, M.D., Russell Van Dyke, M.D.

**Antiviral Drugs Advisory Committee Member (Non-voting):**

Joseph Camardo, M.D. (Industry Representative)

**Antiviral Drugs Advisory Committee Members Not Present (Voting):**

Curtis Hagedorn, M.D., Tracy Swan (Consumer Representative)

**Special Government Employee Consultants Present (Voting):**

Michael Bigby, M.D., Elizabeth Connick, M.D., Lynda Dee (Patient Representative), Lawrence Freedman, M.D., Marc Ghany, M.D., M.H.S.c., Thomas Giordano, M.D., M.P.H., Robert Knodell, M.D., Louis Korman, M.D., Yoshihiko Murata, M.D., Ph.D., Pritybala (Tina) Valbh, R.Ph, Kathleen Young (Acting Consumer Representative)

**FDA Participants (Non-voting):**

Edward Cox, M.D., M.P.H., Debra Birnkrant, M.D., Linda Lewis, M.D., Russell Fleischer, P.A.-C., M.P.H.

**Designated Federal Officer:** Paul Tran, R.Ph

**Open Public Hearing Speakers:**

Martha Saly, Director, National Viral Hepatitis Roundtable  
Tracy Swan, Treatment Action Group  
Lorren Sandt, Executive Director, Caring Ambassadors Program, Inc.  
Michael Ninburg, Executive Director, Hepatitis Education Project  
Jules Levin, National AIDS Treatment Advocacy Project (NATAP)  
Colin Schwartz, Manager, National Alliance of State and Territorial AIDS Directors (NASTAD)  
Paul Brayshaw, Co-Chair, People with Bleeding Disorders and HCV  
Sonia Spangenberg R.N, Health Educator, Quantico Naval Health Clinic  
Michael Casey  
KellyAnn Mann Hester

***The agenda was as follows:***

<i>Call to Order and Introductions</i>	<b><i>Victoria A. Cargill, M.D., M.S.C.E.</i></b> <i>Committee Acting Chair, AVDAC</i>
<i>Conflict of Interest Statement</i>	<b><i>Paul Tran, R.Ph</i></b> <i>Designated Federal Officer, AVDAC</i>
<i>Introduction/Background</i>	<b><i>Debra B. Birnkrant, M.D.</i></b> <i>Director</i> <i>Division of Antiviral Products (DAVP)</i> <i>Office of Antimicrobial Products (OAP)</i> <i>Office of New Drugs (OND)</i> <i>Center for Drug Evaluation &amp; Research (CDER)</i> <i>Food and Drug Administration (FDA)</i>
<i>Sponsor Presentation</i>	<b><i>Vertex Pharmaceuticals., Inc.</i></b>
<i>Introduction</i>	<b><i>Robert S. Kauffman, M.D., Ph.D.</i></b> <i>Chief Medical Officer, Clinical</i> <i>Vertex Pharmaceuticals, Inc.</i>

*Hepatitis C Virus — Disease  
Background and Treatment  
Landscape*

**Ira M. Jacobson, M.D.**  
*Chief, Division of Gastroenterology and Hepatology  
Weill Medical College of Cornell University*

*Development Program Overview*

**Robert S. Kauffman, M.D., Ph.D.**  
*Chief Medical Officer, Clinical  
Vertex Pharmaceuticals, Inc.*

*Phase 3 Efficacy*

**Shelley George, M.D.**  
*Vice President, HCV Therapeutic Area Lead  
Vertex Pharmaceuticals, Inc.*

*Safety*

**Priya Singhal, M.D., M.P.H.**  
*Senior Director, Global Patient Safety  
Vertex Pharmaceuticals, Inc.*

*Benefit Risk Assessment*

**Robert S. Kauffman, M.D., Ph.D.**  
*Chief Medical Officer, Clinical  
Vertex Pharmaceuticals, Inc.*

*Clarifying Questions from the  
Committee to Sponsor*

**Break**

**Presentation**

**FDA**

**Russ Fleischer, PA-C, M.P.H.**  
*Senior Clinical Analyst  
Division of Antiviral Products (DAVP)  
OAP, OND, CDER, FDA*

**Pravin Jadhav, Ph.D.**  
*Pharmacometrics Team Leader  
Office of Clinical Pharmacology (OCP)  
Office of Translational Sciences (OTS)  
CDER, FDA*

*Clarifying Questions from the  
Committee to FDA*

**Lunch**

*Open Public Hearing Session*

*Questions from Committee to  
Sponsor and FDA*

Charge to Committee

**Debra B. Birnkrant, M.D.**  
Director  
Division of Antiviral Products (DAVP)  
OAP, OND, CDER, FDA

Discussion/Questions to the  
Committee

**Adjournment**

**Questions to the Advisory Committee:**

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?

*Committee Discussion:* The committee agreed that the expectation of side effects (such as rash) is common with new drugs coming forward, especially for the treatment of life-threatening illnesses, and that risks and benefits must be weighed. The overwhelming consensus of the committee was that the risk did not outweigh the benefit 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.

Please see transcripts for details of committee's discussion.

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

**VOTE:        Yes: 18        No: 0        Abstain: 0**

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

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

**Committee Discussion:** *There was a ringing endorsement from the committee in support of Response-Guided Therapy (RGT) for treatment-naïve patients. The committee was less clear regarding their support for prior relapsers. The committee expressed concern regarding patients with other underlining characteristics such as cirrhosis, patients with higher viral load, patients over 65 years of age. The committee agreed that stronger studies are needed for the prior relapsers and the current data is not as robust for this subset of population.*

*Please see transcripts for details of committee's discussion.*

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?

**Committee Discussion:** *The committee agreed that there is a need for further studies in several populations including individuals with gout and tuberculosis (TB). There were questions regarding the efficacy in Blacks/African Americans as well as in patients with cirrhosis. A need for additional information regarding patients who are over 65 years of age and null responders with cirrhosis was also noted.*

*Please see transcripts for details of committee's discussion.*

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

**Committee Discussion:** *The implication of resistance was of great concern to some panel members as well as cross resistance to other medications and class wide resistance. Studies are necessary for non-responders using pegylated inteferon for genotypes other than type 1. In addition, the committee also had concerns regarding how individuals in the real world will be asked to manage anemia and rash. Food-drug interaction studies such as with grapefruit juice were recommended. More studies of those 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 look at the appropriate dose of Telaprevir with other HIV drugs and the interaction of IL28b and would it be helpful and predictive. The committee felt that there is an opportunity to look at the twice daily dose (BID) versus the three times per day dosing (TID) to improve adherence and compliance to therapy. Use with oral contraceptives is another issue of concern and an area to be studied further.*

*Please see transcripts for details of committee's discussion.*

*The meeting was adjourned at approximately 4:02 p.m.*