

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

**Summary Minutes of the Antiviral Drugs Advisory Committee
April 27, 2011**

Topic: The committee discussed a new drug application (NDA) 202-258, boceprevir (a hepatitis C virus protease inhibitor), manufactured by MERCK & Co., 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 27, 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 27, 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 27, 2011

The following is the final report of the Antiviral Drugs Advisory Committee meeting held on April 27, 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.

The Antiviral Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 27, 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 Merck & Co., 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 8 speakers for the Open Public Hearing session.

Issue: The committee discussed a new drug application (NDA) 202-258, boceprevir (a hepatitis C virus protease inhibitor), manufactured by MERCK & Co., 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):

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., Geraldine Schechter, M.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., Jeffrey Murray, M.D., M.P.H., Mary Singer, M.D., Ph.D., Poonam Mishra, M.D.

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)
Murray C. Penner, BSW, Deputy Executive Director, National Alliance of State and Territorial AIDS Directors (NASTAD)
Paul Brayshaw, Board President, Hemophilia Federation of America
Pamela Belperio, Pharm.D., BCPS, AAHIVE, VA Center for Quality Management in Public Health, Departments of Veterans Affairs

The agenda was as follows:

Call to Order and Introductions

Victoria A. Cargill, M.D., M.S.C.E.
Committee Acting Chair
Antiviral Drugs Advisory Committee
(AVDAC)

Conflict of Interest Statement

Paul Tran, R.Ph
Designated Federal Officer
AVDAC

Introduction/Background

Debra B. Birnkrant, M.D.
Director
Division of Antiviral Products (DAVP)
Office of Antimicrobial Products (OAP)
Office of New Drugs (OND)
Center for Drug Evaluation & Research
(CDER) Food and Drug Administration
(FDA)

Jeffrey Murray, M.D., M.P.H.
Deputy Director
DAVP, OAP, OND, CDER, FDA

Sponsor Presentation

Merck & Co., Inc.

Introduction

Laurie MacDonald, M.D.
Senior Director, Global Regulatory Affairs
Merck & Co., Inc.

Clinical Efficacy

Jan Albrecht, Ph.D.
Vice-President, Clinical Research Hepatology
Merck & Co., Inc.

Clinical Safety and Resistance

Clifford Brass, M.D., Ph.D.
Executive Director, Clinical Research
Merck & Co., Inc.

***Clarifying Questions from the Committee
to Sponsor***

Break

Presentation

FDA

Poonam Mishra, M.D.
Medical Officer
Division of Antiviral Products (DAVP)
OAP, OND, CDER, FDA

Jeffrey Florian, Ph.D.
Pharmacometrics Reviewer
Division of Pharmacometrics
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***

Break

Discussion/Questions to the Committee

Adjournment

Questions to the Advisory Committee:

1. Please comment on the safety of boceprevir in patients with chronic hepatitis C genotype 1, focusing mainly on the hematological effects of boceprevir in combination with pegylated interferon and ribavirin (PR).

Committee Discussion: *There was a general consensus that the increases in hematological adverse effects (AE) seen with Boceprevir appeared to be manageable with multiple options available for remedy. In terms of anemia, reducing the dose of ribavirin would be the first step, then the addition of conventional anemia treatments, as necessary. The committee felt that although Boceprevir offers a great advance in hepatitis C treatment, patient selection would be very important factor. Several panel members expressed concern regarding neutropenia and the potential distribution among a larger patient population. The AEs might be much more profound, but overall these AEs were manageable and again, the committee stressed that patient selection is the key. The committee also indicated that education for both patients and healthcare providers is extremely important since many future treating physicians are more likely to be generalists rather than specialists in the field of hepatitis.*

Please see transcripts for details of committee's discussion.

2. Considering the overall potential risk and benefits of boceprevir, do the available data support approval of boceprevir for treatment of 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 the evidence for use of boceprevir in combination with pegylated interferon/ribavirin in prior null responders (defined as less than 2 log₁₀ decrease in HCV RNA at 12 weeks during previous course of PR therapy), who were not included in the Phase 3 trial, P5101 in subjects who had previously failed PR therapy.

Committee Discussion: *The committee was divided from the outset of the discussion regarding null responders. In addition to safety issues, some of the committee members expressed concern regarding the potential outcomes including the development of viral resistance to boceprevir, which would greatly minimize treatment options for this population. Several of the hepatologists on the panel were minimally concerned with treatment of this population and felt that treatment should be individualized for null responders and should take into account the patient's clinical picture. Other panel members felt that null responders should either not be treated with boceprevir or treated with extreme caution. There was also mention of using a registry to capture further data in this population of patients.*

Please see transcripts for details of committee's discussion.

4. Please comment on the strength of the evidence to support response-guided therapy (RGT) with boceprevir in combination with pegylated interferon and ribavirin. Should certain groups of patients receive longer durations of boceprevir plus PR therapy than that evaluated in RGT arms?

- a. Treatment-naïve patients with detectable HCV RNA at Week 8 and undetectable at Week 24 (late responders)
- b. Patients such as blacks or those with advanced fibrosis or cirrhosis
- c. Null responders (if recommended for inclusion in the indication)

Committee Discussion: *After a lengthy discussion, several points emerged from the discussion:*

1. *The population of patients in the questions 4a, b and c would be a good jump off points for additional studies that the FDA would want to explore.*
2. *Some of the data reviewed by the sponsor indicated that some of these differences for Blacks/African Americans are really a function of the analysis.*
3. *The committee still felt a certain amount of discomfort in making a firm recommendation regarding null responders with some members expressing that clinicians should be free to make treatment decisions and that we don't want to err on being too short with the treatment duration while other members commented that there was not enough information to make this decision.*

Please see transcripts for details of committee's discussion.

5. In addition to pediatric studies, are there any other postmarketing studies you would recommend to further define risks or optimal use of boceprevir in clinical practice?

Committee Discussion: *The committee recommended drug-drug interaction studies with HIV medications, antidepressants, milk thistle, buprenorphine and methadone as additional postmarketing studies. Specific populations such as racial and ethnic minorities to include Blacks/African Americans and Latinos, as well as individuals who have bleeding disorders, null responders, cirrhosis patients, and patients co-infected with hepatitis B + C. In addition, infected individuals who are post-transplant and are taking immunosuppressants should be further studied. The committee agreed that there is a need for studies in patients over the age of 65, especially with the recent data on hepatoma. There was also mention of studying different genotypes.*

Please see transcripts for details of committee's discussion.

The meeting was adjourned at approximately 4:40 p.m.