Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE CDER ANTIVIRAL DRUGS ADVISORY COMMITTEE

March 11, 2005

Members Present (Voting)
Janet Englund, M.D. (Chair)
John Bartlett, M.D.
Victor DeGruttola, Sc.D.
Lauren Wood, M.D.
Victoria Johnson, M.D.
Kenneth Sherman, M.D., Ph.D.
Douglas Fish, M.D.
Ronald Washburn, M.D.
John Gerber, M.D.
Richard Haubrich, M.D.
Lynn Paxton, M.D., M.P.H.
Robert Munk, Ph.D. (Consumer Representative)

FDA Participants
Mark Goldberger, M.D., M.P.H.
Debra Birnkrant, M.D.
Linda Lewis, M.D.
James Farrelly, Ph.D.

Executive Secretary
Anuja M. Patel, M.P.H.

Consultants to the Antiviral Drugs Advisory Committee (Voting)
Beth Bell, M.D., M.P.H.
Ronald Herbert, D.V.M., Ph.D.
Kathleen Schwarz, M.D.
Leonard Seeff, M.D.
Samuel So, M.D.
Brett Grodeck (Patient Representative)

Antiviral Drugs Advisory Committee Industry Representative (Non-voting)
Eugene Sun, M.D.

These summary minutes for the March 11, 2005, meeting of the Antiviral Drugs Advisory Committee were approved on March 16, 2005.

I certify that I attended the March 11, 2005, meeting of the Antiviral Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

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Anuja Patel, M.P.H.
Executive Secretary

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Janet Englund, M.D.
Chair

Open Public Hearing Speakers
There were no registered speakers for the open public hearing.

FDA Presentations:

Overview of Issues	Debra B. Birnkrant, M.D. Director, Division of Antiviral Drug Products (DAVDP)
Carcinogenicity Issues	James G. Farrelly, Ph.D. Pharmacology Team Leader, DAVDP
Clinical Issues	Linda L. Lewis, M.D. Lead Medical Officer, DAVDP

Sponsor Presentations: Bristol-Myers Squibb Company

Introduction	Elliott Sigal, M.D., Ph.D. Chief Scientific Officer & President, Pharmaceutical Research Institute
Background	Richard Colonno, Ph.D. Vice President, Infectious Diseases Drug Discovery
Nonclinical Safety	Lois Lehman-McKeeman, Ph.D. Distinguished Research Fellow, Discovery Toxicology
Clinical/Efficacy and Safety	Evren Atillasoy, MD Director, US Medical Affairs
Resistance	Richard Colonno, Ph.D. Vice President, Infectious Diseases Drug Discovery
Benefit vs. Risk Assessment	Donna Morgan Murray, Ph.D. Executive Director, Global Regulatory Sciences

Questions to the Committee:

1. How would you assess the risk-benefit of ETV in the context of the available clinical safety, efficacy, resistance, and non-clinical carcinogenicity data?

Given the caveat that additional studies on pediatric population and long term follow up in relation to carcinogenicity should be explored, the overall consensus of the Committee was that the overall risk-benefits is positive and that the benefits outweigh the risks. The committee was impressed by the efficacy, clinical safety, and resistance data. The Committee commended the Sponsor and the Agency for their detailed and thorough analysis.

In addition, the committee has concerns about resistance and details about the pharmacovigilance studies. The Committee appreciated the carcinogenicity data in the animal models. The committee advised the Agency to encourage post marketing studies and surveillance and include the African-American population.

2. A. Does the risk-benefit assessment for entecavir support the approval of entecavir for the treatment of chronic HBV in adult patients?

Yes = 18 No= 0 Abstain= 0

B. If the answer to #2A is no, what information would be needed to support a resubmission?

The committee voted unanimously yes to question 2A.

3. A. If the answer to #2A is yes, discuss whether the results of the rodent carcinogenicity studies should impact the Indication and Usage section of product labeling.

The committee advised the Agency that the carcinogenicity data does not warrant a black box warning. The committee made several suggestions to the Agency including mentioning animal carcinogenicity in an insert. The Committee encouraged labeling for a first line defense, and possible use in combination therapy.

B. Based on the available data, discuss the potential role of entecavir in the HBV treatment armamentarium.

There was universal acclamation for usage of entecavir as a second-line defense for lamivudine resistant patients.

4. A. Assess the potential risks and benefits of proceeding with development of entecavir for the treatment of chronic HBV in pediatric patients.

The committee encouraged the Sponsor to continue pediatric developing studies and including pharmacokinetic studies due to off-labeling use of the oral solution dosage form in pediatric patients. Additional pediatric studies with long-term follow up are vital.

B. What, if any, additional information is needed in order to proceed?
The committee was concerned about off-label use of entecavir in pediatric patients; however, approval of the oral suspension due to the need of this form of drug in patients with renal dysfunction and geriatric populations was encouraged. The committee felt there was a need for additional data in the pediatric population, as well as more animal studies in young animals. The committee advised the Agency to conduct Phase 1 studies in young children at the same time as carcinogenicity and toxicology studies in animals.

5. Discuss the applicant's proposed pharmacovigilance plan to address human cancer risk, including comments on the design of the proposed large simple study.

The committee felt that a randomized study design is the best design and that the biggest risk of the study is the lack of enrollment and crossing over of patients. The committee expressed the need for long-term study endpoints. Concern about the feasibility of such a study was discussed.

6. Are there other issues that you would like to see addressed through post-marketing commitments?

The committee suggested resistance analysis be addressed in post-marketing studies. In addition, the committee encouraged the sponsor to conduct trials on dosing regimes. Long term follow-up in patients on entecavir should be initiated to monitor interaction with other HBV treatments and possible tumor development.

See transcript for details.

The Chair summarized the discussion in that the data the Sponsor submitted was well documented and robust, sufficiently researched, and with an overall favorable risk-benefit. The Chair felt that optimal duration of studies was still in question and there was an immediate need for additional studies in the pediatric population. Additionally, the need for long-term follow-up was important to evaluate potential resistance in patients.

Following the discussion session, the meeting adjourned at approximately 3:30 PM.