Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE CDER ANTIVIRAL DRUGS ADVISORY COMMITTEE

May 19, 2005

Members Present (Voting)
Janet Englund, M.D. (Chair)
Maribel Rodriguez-Torres, M.D.
Victor DeGruttola, Sc.D.
Lauren Wood, M.D.
Kenneth Sherman, M.D., Ph.D.
Ronald Washburn, M.D.
John Gerber, M.D.
Robert Munk, Ph.D. (Consumer Representative)

FDA Participants
Mark Goldberger, M.D., M.P.H.
Debra Birnkrant, M.D.
Rosemary Johann-Liang, M.D.
Andrea James, M.D.

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

Members Present (Non-voting)
Douglas Fish, M.D.
Richard Haubrich, M.D.

Consultants to the Antiviral Drugs Advisory Committee (Voting)
Robert Grant, M.D., M.P.H
Veronica Miller, Ph.D.
Frank Maldarelli, M.D., Ph.D
Gene Morse, Pharm.D., FCCP, BCPS
Edmund Capparelli, Pharm.D.
Stephen Hall, Ph.D.

Consultants to the Antiviral Drugs Advisory Committee (Non-voting)
Princy Kumar, M.D.

Antiviral Drugs Advisory Committee Patient Representative (Non-voting)
Lynda Dee, J.D.

Antiviral Drugs Advisory Committee Industry Representative (Non-voting)
There was no Industry Representative at this meeting.

These summary minutes for the May 19, 2005, meeting of the Antiviral Drugs Advisory Committee were approved on __June 7, 2005_____.

I certify that I attended the May 19, 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 Speaker
Mr. Rob Camp
Treatment Action Group
New York, New York

Sponsor Presentations: Boehringer Ingelheim Pharmaceuticals, Inc.

• Introduction	Burkhard Blank, M.D. Senior Vice President Medicine/DRA
• Tipranavir Development	Douglas Mayers, M.D. International Head, Therapeutic Area Virology
• Efficacy and Drug: Drug Interactions	Scott McCallister, M.D. Global Medical Team Leader, TPV
• Safety	Christopher Corsico, M.D. Head, Drug Surveillance and Information
• Resistance	Douglas Mayers, M.D. International Head, Therapeutic Area Virology
• Potential Utility of Tipranavir In Current Clinical Practice	Daniel Kuritzkes, M.D. Director of AIDS Research, Brigham and Women's Hospital, Division of AIDS, Associate Professor of Medicine, Harvard Medical School
• Conclusions	Burkhard Blank, M.D. Senior Vice President Medicine/DRA

FDA Presentations: Division of Antiviral Drug Products

• Efficacy Evaluation	Rafia Bhore, Ph.D. Statistical Reviewer
• Resistance Evaluation	Lisa Naeger, Ph.D. Senior Microbiology Reviewer
• Exposure-Response Data	Jenny J. Zheng, Ph.D. Pharmacometrics Reviewer
• Drug Interactions	Yuanchao (Derek) Zhang, Ph.D. Clinical Pharmacology and Biopharmaceutics Reviewer
• Safety Profile and Conclusions	Andrea James, M.D. Medical Reviewer

Questions to the Committee:

Question 1:

- Do the data demonstrate that tipranavir/ritonavir (TPV/r) is safe and effective for the multi-drug resistant HIV-1 infected population?

Yes = 11 No = 3 Total Votes = 14

- If no, what additional data are needed to provide evidence of safety and efficacy?

Members that voted "no" felt that additional data providing evidence of safety and efficacy was needed. Data including long term efficacy data, drug interaction, and liver toxicity data were among the suggestions. Substantial concerns regarding hepatic toxicity in this patient population were raised by committee members. Overall the committee advised the Agency that additional long- term follow-up was needed, specifically, in the female population.

- If yes, please address the appropriate population for TPV/r use considering the following:
  - limited inclusion criteria of the RESIST trials
  - drug-drug interactions
  - resistance information and patterns associated with optimal use
  - safety considerations

Members who voted "yes" felt that the need for the drug in this patient population was great; however, members expressed concerns with need for long term follow-up and toxicity management by specialists. Members urged the sponsor and the agency to explore drug-drug interactions, including interactions with lipid lowering agents, contraceptives, and cardiac drugs. The committee suggested that future studies include women with rash, liver failure patients, and toxicology.

Please see transcript for additional details

Question 2:

- Given the data on transaminase elevations, please provide your recommendations for:
  - TPV/r use in patients with underlying liver disease
  - Monitoring and management of hepatotoxicity during clinical use
  - Future studies

Close follow up of patients receiving this therapy and long-term follow up in enrolled study patients for hepatic toxicity were suggested. Specific suggestions for future studies included the evaluation of more Hep B/C + patients and those entering treatment with slightly higher LFT's (such as grade 2). The hepatologists on the panel were concerned that no liver biopsy data was available and strongly recommended that such studies be considered in the future. Because the correlation of fibrosis and transaminase elevation is not perfect, concerns were expressed about the increased risk for disease in those patients with fibrosis already present.

Question 3:

- The limited amount of data in females with HIV infection in the TPV program shows an increased incidence of rash in females. Please provide your recommendations for:
  - Investigation of this safety signal in future studies with TPV

The committee was concerned about an insufficient amount of data in women in pivotal clinical trials, particularly when the signal of skin rash was noted early. Recommendations for further studies with women and diverse contraceptive methods were recommended.

Please see transcript for details

Question 4:

- Current information indicates the net effect of TPV/r on substrates of CYP1A2, CYP2C9, CYP2C19 and CYP2D6 is not known, and there are competing effects of TPV/r on CYP3A (inhibition) and P-glycoprotein (induction). Please comment on additional post-marketing drug interaction studies.

The committee suggested post-marketing drug interactions studies using cocktail studies to evaluate mechanisms of inhibition and induction. These studies should evaluate the impact of TPV/r on various transporter systems including PGP as well as MRP's. Specific interactions using digoxin, proton pump inhibitors, dual PI's, calcineurin inhibitors, and statins were recommended. Other panel members recommended studies of phenytoin, midazolam, and tenofovir as common agents in use in these patients.

Question 5:

- Given the high inter-patient variability in TPV exposures following fixed doses and exposure (blood levels)-virologic response relationships, could a biomarker such as Cmin/IC50 be used for the individualization of TPV/r therapy? Please discuss the studies that would supplement the data presented today.

Although the committee was very interested in the possibility of therapeutic drug monitoring for the individualization of patient care with potentially toxic drugs, the committee as a whole felt there was not enough data to recommend this at the current time.

See transcript for additional details

Question 6

- Please provide your recommendations regarding the display of TPV/r resistance data/analyses in the TPV package insert that would be useful to clinicians.

Simple but complete representation of available data was discussed, with several specific designs suggested. Recommendations for serial evaluation of hepatic function were also discussed.

Question 7:

- Please discuss and recommend future study designs /data acquisition for the heavily pretreated population.

The Committee suggested incorporating real time phenotypes in future studies and exploring possible mutations in the patient population. Incorporation of at least two novel PI's in treatment studies was recommended, with potential studies evaluating two or more investigational agents (including those from different manufacturers)were also encouraged. Although collecting better data on clinical endpoints was highly encouraged and such data was felt to be useful, it was acknowledged that studies using surrogate markers will be necessary in evaluating salvage studies in this patient population. Study designs including open label drug and rollover to experimental arms after relatively short periods may be necessary for practical and ethical reasons.

Following the discussion session, the meeting adjourned at approximately 5:00 PM.