Antiviral Drugs Advisory Committee
DRAFT MINUTES
August 6, 2002

The Antiviral Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on August 6, 2002 at the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland. There were approximately 250 people in attendance. The meeting was chaired by Roy M. Gulick, M.D., M.P.H.

The Committee discussed NDA 21-449, adefovir dipivoxil tablets, sponsored by Gilead Sciences, Inc., proposed for treatment of chronic hepatitis B infection. The Committee had received a briefing document from both Gilead Sciences, Inc. and the FDA Division of Antiviral Drug Products.

The meeting was called to order at 8:00 a.m. by Roy M. Gulick, M.D., M.P.H., Chair. The Committee members, consultants, guests, and FDA participants introduced themselves. The Conflict of Interest Statement was read by Tara P. Turner, Pharm.D., Executive Secretary of the Antiviral Drugs Advisory Committee.

Opening remarks were given by Debra B. Birnkrant, M.D., Director, Division of Antiviral Drug Products.

Gilead Sciences, Inc. made the following presentation:

Evaluation of Liver Histology in Clinical Trials for Chronic Viral Hepatitis	Zachary D. Goodman, M.D., Ph.D.
Introduction Chronic Hepatitis B Pre-Clinical Clinical Pharmacokinetics	Alan Taylor, Ph.D.
Clinical Efficacy and Safety Pivotal Studies Supportive Studies Future Studies	Carol Brosgart, M.D.

The FDA made the following presentation:

Patient Demographics Efficacy Data Assessment	Rafia Bhore, Ph.D.
Safety Data Assessment	Tan Nguyen, M.D., Ph.D.

Viral Resistance

During the Open Public Hearing portion of the meeting presentations were made by the following registered speakers:

Rochelle Yedvarb
Elias Anastasopoulos
Larry Kramer
Alan P. Brownstein, M.P.H.

Debra B. Birnkrant, M.D., gave the Charge to the Committee. The Committee was then asked to address the following list of questions:

Questions to the Committee

1. Has the applicant demonstrated the safety of adefovir 10-mg in patients with chronic hepatitis B (CHB)? Please discuss patients with decompensated liver disease and/or baseline renal insufficiency. Also include in your discussion proposals for patient monitoring of adefovir-associated toxicity.

A formal vote was taken and the results were as follows:

Yes=14 No=0 Absent=1

In general the Committee felt that the applicant had demonstrated safety for 48 weeks in patients with normal renal function. The Committee expressed discomfort with the lack of long term safety data especially since the treatment duration has not been determined. Treatment with this drug might be indefinite. Longer term treatment holds increased risk of nephrotoxicity. There are unanswered questions about whether the renal toxicity is cumulative and whether it is reversible. Suggestions for monitoring included following the serum creatinine every 4-8 weeks in patients with baseline abnormal renal function (every 3 months is more appropriate for patients with baseline normal renal function). Some members expressed discomfort with the nomogram for dose adjustment in renal dysfunction and suggested that it needs to be refined. Concerns were expressed about the use of adefovir in patients with decompensated liver disease as well as in patients with other co-morbidities (i.e. HIV co-infection) because of the potential interactions with other nephrotoxins. Concerns were raised about the possibility of "hepatic flare" when patients stop taking the drug and the need to monitor for this reaction. Suggestions for monitoring included following the liver enzymes and PT monthly after discontinuation of the drug and possible tapering rather than abrupt discontinuation. It was proposed that data correlating drug levels with toxicities would be helpful in determining how to monitor patients.

2. Has the applicant demonstrated the efficacy of adefovir 10-mg for the treatment of CHB? Please comment on the efficacy in patients with the following characteristics: compensated liver disease; decompensated liver disease; lamivudine resistance disease; presumed precore mutant disease; and co-infection with HBV and HIV.

A formal vote was taken and the results were as follows:

Yes=15 No=0

In general, the Committee felt that the applicant has demonstrated effectiveness in the 48 week period in patients with compensated liver disease. Regarding the supportive studies that were conducted in patients with decompensated liver disease, it was felt that the drug probably works but efficacy was not demonstrated because HBV DNA was measured as opposed to histologic changes. It was felt that there is insufficient data to support a specific indication in HIV/HBV coinfected patients. Response rates in the cirrhotic patient population are also needed.

3. Based on the risk/benefit profile of adefovir, does the Committee recommend approval of adefovir (10-mg daily) for the treatment of CHB in adults?

A formal vote was taken and the results were as follows:

Yes=15 No=0

4. Are there any issues with the safety and efficacy data that should be highlighted in the product labeling? In particular, please discuss the use of adefovir in HIV/HBV coinfection and the potential risk of inducing NRTI resistance.

The Committee felt that the issue of resistance is unclear at this time. We don't yet know if there is HBV resistance to adefovir. It is encouraging that no mutations appeared in the 48 week studies but more needs to be done. We don't know the effect of low dose adefovir on HIV resistance. Practitioners should be warned that when the drug is stopped there is the risk of a "flare" resulting in major elevations of the liver enzymes. Although the study period was 48 weeks it doesn't mean that the recommended duration of treatment is 48 weeks and this should be conveyed in the label. The potential for cumulative nephrotoxicity should be described in the label. Concerns were raised that there is no clinical data to support the nomogram proposed by the applicant for dosing in renal insufficiency. There was some debate as to whether liver biopsy should be required prior to initiating therapy with adefovir. The consensus of the experts was that a baseline biopsy should be strongly recommended but not required and they felt that perhaps this could be addressed by practice guidelines rather than the product labeling.

5. Please recommend appropriate Phase 4/postmarketing studies for adefovir in CHB patients. In particular, please discuss the adequacy of the applicant's current program to detect adefovir-resistant HBV and the optimal strategy for long-term resistance surveillance.

It was suggested that adefovir should be studied in special patient populations such as African Americans, Hispanics, and pregnant women. Because of the threat of the development of resistant HBV, combination therapy (i.e. with lamivudine) should be studied. Phenotypic and genotypic evaluations need to be conducted to evaluate resistance. The optimal duration of treatment needs to be established. The drug interaction profile is not well understood. Drug-drug interactions need to be carefully characterized (esp. with ibuprofen, DDI, cyclospoprine, tacrolimus, and protease inhibitors).

The meeting adjourned at 5:35 p.m.