CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: JOINT ANTIVIRAL DRUGS ADVISORY COMMITTEE and OPHTHALMIC DRUGS SUBCOMMITTEE

DATE OF MEETING: 03/14-15/96

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SUMMARY MINUTES

Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ANTIVIRAL DRUGS ADVISORY COMMITTEE
AND
OPHTHALMIC DRUGS SUBCOMMITTEE (DODAC)

March 14 (Antiviral only) and 15, 1996
Holiday Inn, Gaithersburg
2 Montgomery Village Avenue
Gaithersburg, MD 20879

Antiviral Drugs Advisory Committee
Fred Valentine, M.D., Chair
Fred Gordin, M.D.
Laurence Freedman, M.A. (3/14)
W. Chris Mathews, M.D.

Voting Consultant (3/15)
Jerrold Ward, D.V.M., Ph.D

Consultants/Guests (3/15)
Kevin Frost
Susan K.F. Keay, M.D., Ph.D.
James Lipsky, M.D.

Ophthalmic Drugs Subcommittee (DODAC) (3/15)
Emily Chew, M.D.
S.James Kilpatrick,Jr.,Ph.D.
Joel Mindel, M.D.
M. Roy Wilson, M.D.

FDA Participants
David Feigal, M.D., M.P.H.
Steven Gitterman, M.D., Ph.D.
Samuel Maldonado, M.D. (3/14)
Kimberly Struble, R.Ph. (3/14)
Wiley Chambers, M.D. (3/15)
James Farrelly, Ph.D. (3/15)
Alan Muhly, Ph.D. (3/15)
Douglas Pratt, M.D. (3/15)

These summary minutes for the March 14 Antiviral Drugs Advisory Committee closed session and the March 15, 1996 joint meeting of the Antiviral Drugs Advisory Committee and the Ophthalmic Drugs Subcommittee (DODAC) were approved on 11/22/96.

I certify that I attended the March 14 Antiviral Drugs Advisory Committee closed session and the March 15, 1996 joint meeting of the Antiviral Drugs Advisory Committee and the Ophthalmic Drugs Subcommittee (DODAC) and that these minutes accurately reflect what transpired.

Rhonda W. Stover, R.Ph.
Executive Secretary

Fred Valentine, M.D.
Chair

CLOSED SESSION-March 14, 1996

The Antiviral Drugs Advisory Committee began their meeting on March 14, 1996 at 1 p.m. with a closed session to discuss trade secret and/or confidential commercial information relevant to pending matters (5 U.S.C. 522b(c)(4)).

OPEN SESSION-March 15, 1996
CALL TO ORDER

The joint meeting of the Antiviral Drugs Advisory Committee and the Ophthalmic Drugs Subcommittee (DODAC) was called to order at 8:30 a.m. by Fred Valentine, M.D., Chair of the Antiviral Drugs Advisory Committee. The topic of the meeting was New Drug Application 20-638, cidofovir intravenous (Vistide®, Gilead Sciences) for treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Background materials provided to committee members included summary packages from the sponsors and reviews from the FDA. The conflict of interest statement was read by Ermona McGoodwin, Executive Secretary. Approximately 200 people were present.

INTRODUCTION

Dr. David Feigal, Director of the Division of Antiviral Drug Products, welcomed the members of the Committee and Subcommittee and thanked them for their participation. A brief review of the history of CMV retinitis agents and product study designs was given. Also, administrative remarks concerning presentation order and meeting purpose were made to the members.

SPONSOR PRESENTATION

Dr. John Martin introduced the sponsor presentation and acknowledged the study investigators and consultants who were also in attendance. Dr. Howard Jaffe discussed the background, preclinical overview, and the Phase I/II clinical program. Significant preclinical findings included nephrotoxicity and adenocarcinomas in female rats.

Dr. Robert Stagg presented data from 2 pivotal trials in AIDS patients: Study 106 of patients with previously untreated

peripheral retinitis (48 patients US & UK) and Study 107 of patients with relapsing retinitis (100 patients US & UK). In addition, Study 120 of treatment IND patients with relapsing retinitis (120 patients US & Canada) and preliminary data on 61 patients from Study 105, a scientifically independent study by SOCA (Studies of Ocular Complications of AIDS, funded by NIH and the Sponsor), were presented. Time to retinitis progression based on photographic assessment was the primary endpoint with cidofovir patients showing delayed disease progression.

Dr. Howard Jaffe presented the Phase IV plans and a risk benefit assessment of cidofovir therapy. Phase IV plans include studies with renal insufficient patients and pediatric patients with CMV end-organ disease. Studies of drug interactions (ddI, TMP-SMX, and fluconazole), the use of intravitreous cidofovir, the effect of cidofovir reinduction, and combination cidofovir IV induction and oral maintenance therapies are also planned or ongoing.

The risk of nephrotoxicity is minimized by the use of probenecid and hydration during cidofovir administration and conservative dosing guidelines. Dr. Jaffe stated that no non-AIDS related malignancies have been observed in study patients followed since May 1992. Furthermore, the incidence of AIDS-related malignancies is consistent with historical controls. The benefits of cidofovir therapy include delayed retinitis progression, antiviral activity against most ganciclovir or foscavir resistant isolates, and an extended dosing interval. Recommended cidofovir dosing is 5 mg/kg body weight x 2 doses, then biweekly. Ganciclovir and foscarnet require 28 to 63 induction infusions and daily infusions thereafter.

FDA PRESENTATION

After a brief introduction by Dr. Douglas Pratt, Dr. James Farrelly presented highlights from the preclinical toxicology studies. In a 26 week study, rats were dosed subcutaneously once a week at 0,0.6,3 or 15mg/kg/week. The low dose was equal to 0.04 times the clinical dose. The first palpable tumor appeared after 6 doses. In females, mammary adenocarcinomas developed at all doses. In males, Zymbal's gland tumors were an occurrence. Cidofovir caused no tumors in a one-year monkey toxicity study. Dr. Farrelly concluded that cidofovir has toxicities similar to

those of nucleoside analogs, is toxic to rapidly dividing cells, is a potent carcinogen in rats, and should be considered a potential human carcinogen.

Dr. Alan Muhly discussed statistical issues from the FDA's analysis of efficacy. Dr. Muhly commented on the designs of study 106 and study 107, with regard to potential bias with open label trials, patient randomization methods, mean baseline characteristics and patient followup. Study 106 and Study 107 were analyzed in terms of the significance of the treatment effect and the magnitude of its clinical significance. Additionally, the robustness of the conclusions was addressed. For Study 106, it was observed that a significant treatment effect in favor of cidofovir exists and is robust. For Study 107, it was observed that a significant dose response favoring the high dose (5mg/kg) exists and is robust although not as strong as for Study 106. The magnitude of the clinical significance of the observed effects was problematic for each study and was not determined to be robust.

Dr. Wiley Chambers provided the review of retinal photography and highlighted slides of questionable readings. It was reiterated that there was no disagreement about the positive treatment effect of Vistide between the applicant and the FDA analysis. However, the magnitude of the effect and the speed with which it occurs was in question. In some patients the disease was quieted and in others, it was totally eradicated. Dr. Chambers stated that final conclusions are not appropriate without a direct comparison in the same trial.

Dr. Pratt commented on the efficacy and safety review and summarized the main points of the FDA analyses. Cidofovir has demonstrated efficacy for the treatment of CMV retinitis in AIDS patients although the estimate of progression time is not robust. Cidofovir has not been directly compared to other approved therapies and its utility for the treatment of systemic disease is unknown. Nephrotoxicity, carcinogenicity, and neutropenia were the major safety concerns with nephrotoxicity being the most serious acute toxicity. Dr. Pratt noted that dosing regimens have been defined to reduce renal toxicity. Dr. Pratt commented on the lack of adenocarcinomas in the studies relative to few women study participants. However, the sponsor's Phase IV commitments include malignancy assessment. Although a clear

relation between infections and neutropenia was not established, neutropenia must be considered a risk factor for infection.

SOCA PRESENTATION

Dr. Kurt Meinart presented preliminary data on 61 patients from Study 105, a scientifically independent study by SOCA (Study of Ocular Complications of AIDS, funded by NIH and the sponsor). Study 105, a multicenter trial with 15 clinics, is a study to assess the relative safety and efficacy of HPMPC (Cidofovir) for treatment of newly diagnosed AIDS-related CMV retinitis. Dr. Meinart informed the Committee that the FDA had not seen this data beforehand and that the data was being presented before it had been thoroughly analyzed and submitted for publication. The inclusion/exclusion criteria, study design, and baseline characteristics, as well as the preliminary study results were presented by Dr. Meinart. Dr. Meinart noted that Study 105 differs from Study 106 in that the decision to treat was made by the clinician with no feedback from the reading center. Preliminary results indicated that a dose response consistent with treatment benefit was observed.

OPEN PUBLIC HEARING

Nine people spoke at the Open Public Hearing, most in support of approval. One supported limiting approval to salvage therapy only.

Mr. Steven Rickard, who disclosed that Gilead paid for his travel, strongly urged the Committee to recommend cidofovir approval. He contrasted his use of other anti-CMV therapies with the improvement in his quality of life due to cidofovir use. Additionally, he stated that there is currently no CMV activity in his eyes and that cidofovir side effects are minimal.

Mr. Peter Kaufman disclosed that Gilead paid for his travel and accommodations. He discussed his suboptimal experiences with oral and IV ganciclovir and his increased quality of life associated with cidofovir use. Furthermore, Mr. Kaufman voiced his concern regarding the TAG (Treatment Action Group) recommendation that cidofovir be used for salvage therapy stating that cidofovir should be approved and made available as soon as possible without restriction.

Ms. Dawn Beckhols disclosed that Gilead paid for her travel expenses. Ms. Beckhols discussed her use of approved anti-CMV therapies relative to the time-consuming IV administration of these agents and the side effects she experienced. She recommended that cidofovir be approved as soon as possible due to the efficacy, the reduction of side effects, and the improved quality of life that she has experienced. Additionally, she told the Committee that she understood that cidofovir may not work forever but that she appreciates the treatment option.

Dr. Gary Blick spoke on behalf of two patients, Andrew and Lou, who were unable to attend the meeting. He shared the history of each patient and the positive therapeutic benefits they experienced by using cidofovir. Dr. Blick stated that he is convinced of the safety and efficacy of cidofovir as well as the significant improvement in quality of life it provides for patients.

Mr. Albert Avendano, Executive Director of the Florida AIDS Action Council in Miami, stated that he represented 6,000 people in the Miami area that are supportive of the rapid approval of cidofovir. Mr. Avendano urged the sponsor to implement responsible Phase IV studies to address questions of carcinogenic effects.

Mr. Joel Martinez, Director and Founder of the Center for AIDS in Houston, Texas, disclosed that Gilead paid for his accommodations. Mr. Martinez stated that the Center supports the approval of cidofovir. The reasons cited for approval were that cidofovir is efficacious in delaying the progression of CMV retinitis, has a manageable side effect profile, improves patients' quality of life, and eliminates the need for an indwelling catheter. Additionally, Mr. Martinez expressed the Center's concerns which include the need for drug interaction studies, extraocular CMV studies, strict and explicit product labeling, and educational programs for physicians and patients.

Mr. Bill Bahlman, of ACT-UP New York's Treatment and Data Committee, disclosed that Gilead paid his travel expenses. Mr. Bahlman agreed with the other public comments in support of cidofovir. He expressed that cidofovir should not be salvage therapy and that its use be unrestricted to avoid reimbursement difficulties.

Mr. Michael Marco, Director of Opportunistic Diseases for the Treatment Action Group-New York, discussed TAG's position paper on cidofovir. The group recommends cidofovir be approved for salvage therapy only. Mr. Marco spoke about the nephrotoxicity associated with cidofovir and the potential for problems with its use by inexperienced clinicians. He also expressed concern about the ethicalness of randomizing patients to no treatment in Phase II and Phase III studies.

Mr. Mark Bray, a clinical nurse specialist for the Seattle Treatment Education Project, disclosed that Gilead paid for his travel expenses. Mr. Bray stated that cidofovir is remarkable and that he supports its approval for all patients who need it. He expressed concern about the approval of cidofovir as salvage therapy due to the potential for reimbursement difficulties.

COMMITTEE DISCUSSION

The Committee discussed all questions and issues that arose from the Sponsor, FDA, and Open Public Hearing presentations and from within the Committee. This discussion was incorporated to vote on the following question:

1. *Do the safety and efficacy data presented support the use of cidofovir (Vistide®) for the proposed indication?*

Vote: 8 yes
0 no

Comments: The Committee expressed concern about the lack of long-term data as well as nephrotoxicity and neutropenia in humans and adenocarcinomas in female rats. They recommended that these issues be addressed in the labeling. One member expressed concern regarding bias in the open label studies.

2. *Please comment on the Sponsor's proposed Phase 4 development plan.*

Comments: The Committee recommended studies be done in women and minorities. Long-term safety data are needed especially to address nephrotoxicity, neutropenia, and tumorigenicity. Additional dosing studies are needed as well as studies on the systemic effects of cidofovir. Comparison and combination therapy

studies along with studies on the development of resistance must be a major part of the development plan.

CLOSING REMARKS

Dr. Feigal thanked the Committee for their work. Also, Dr. Feigal thanked Ermona McGoodwin, Executive Secretary, for assisting the Antiviral Committee in addition to her other committees and welcomed Rhonda W. Stover, the new Executive Secretary for the Committee.

Dr. Valentine concluded the meeting at 3:50 p.m.