Antiviral Drugs Advisory Committee

DRAFT MINUTES

March 19, 2002

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The Antiviral Drugs Advisory Committee of the Food and Drug Administration, Center for 1)rug Evaluation and Research, met on March 19, 2002 at the Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland. There were approximately *350* people in attendance. The meeting was chaired by Roy M. Gulick, M.D., M.P.H.

The Committee discussed NDA 21-245, Picovir (pleconaril), sponsored by ViroPharma, Incorporated, proposed for treatment of acute picornaviral upper respiratory illness (common cold) in adults. The Committee had received a briefing document from both ViroPharma, Incorporated 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.

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

VircPharma, Incorporated made the following presentation:

Introduction: Mark McKinlay, Ph.D.
Impact of the Common Cold: Frederick G. Hayden, M.D.
A New Option for Treating Colds: Mark McKinlay, Ph.D.
Clinical Efficacy and Safety: Ellen C. Cooper, M.D., M.P.H.
Benefit/Risk: Ellen C. Cooper, M.D., M.P.H.

The FDA made the following presentation:

Overview of NDA and Issues: Russ Fleischer, PA-C, M.P.H.
Statistical Review of Efficacy: Thomas Hammerstrom, Ph.D.
Safety and Summary: Russ Fleischer, PA-C, M.P.H.

There were no speakers for the Open Public Hearing portion of the meeting.

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. Please discuss the efficacy of pleconaril for treatment of acute VRI in adults. Please consider the following points as you discuss this issue:
• the efficacy results from studies 843-043 and 843-044
• the efficacy results across the phase 2 studies
• the manner in which pleconaril will likely be used in clinical practice
• prescribed to symptomatic patients with no rapid diagnostic test available to identify infected patients
• prescribed to asymptomatic patients with intention for self initiation at onset of symptoms
• the need to administer pleconaril with food
• the need to institute pleconaril within 24 hours of onset of the first symptoms
• the efficacy results in smokers
The committee agreed that efficacy has been demonstrated, but that the documented treatment effect is modest at 0.5-1 day. The committee expressed concerns about the generalizability of the study results due to the fact that the studies were conducted in a small homogeneous population. Concern was expressed about the lack of data in pediatric patients, who are known to get the most colds. It was also noted that there is no data in at risk patients (i.e. immunocompromised patients, elderly). Of similar concern is the lack of benefit in smokers. While clinical efficacy (primary endpoint) has been shuwn, there is no evidence of virologic efficacy and this requires further study. Some members thought that more emphasis should be given to functional measures (i.e. time lost from work/school). It was also suggested that it might be helpful to measure the effect of the drug on complications of the common cold O.e. otitis media).
The committee was very concerned that the drug has to be taken within 24 hours of the onset of symptoms. This was felt to be very impractical in real l4fe. Some members predicted that patients would get prescriptions filled at the beginning of the cold season to self initiate treatment at the onset of symptoms. This was described as analogous to an OTC situation, which offers great potential for inappropriate use.
Regarding the need to administer pleconaril with food, it was suggested that more information is needed about the type of meal or snack that is required in order to develop meaningful recommendations for prescribers and consumers.

2. Please discuss the safety of pleconaril in adult patients with symptoms of acute VRI. Please consider the following points as you discuss this question:
• pleconaril's effect on cytochrome CYP3A4
• the frequency of menstrual disorders occurring in females using OCs while being treated with pleconaril, and the potential risk for unintended pregnancy
• the apparent pharmacodynamic interaction with theophylline. The reports of tachycardia and palpitations reported in otherwise healthy patients treated with pleconaril
• the general types and frequencies of adverse events observed in clinical studies
Overall the Committee felt that the risk/benefit ratioforpleconaril in the treatment of the common cold is not there. Members stated that for an acute self-limited illness the bar for safety must be raised to a higher standard. Only 50% of the study population were infected with picornavirus.

Therefore, there are a large number ofpeople who are not expected to benefit from taking this drug at alL They will be exposed to unnecessary risk Even in those who might benefit, the modest treatment effect is outweighed by the lack of safety information. Also, f the drug is given too late (i.e. outside of the 24 hour window) the patient is exposed to risk in exchange for no benefit. The predicted usage pattern for this drug was especially concerning to the Committee. It was predicted that the drug would likely be used in an OTC type of situation where patients would obtain prescriptions in advance with the intent of self initiating treatment at the onset of symptoms. The lack of safety information is further compounded under this circumstance because of the lack offace-to-face interaction between the physician and the patient. There is incomplete information about potential drug interactions with pleconaril. The committee was uncomfortable with making this drug widely available without having a thorough understanding of its effect on CYP3A4. Concerns were raised about the risks of pregnancy and breakthrough vaginal bleeding in women taking oral contraceptives. More viral resistance studies were recommended. Some members were concerned about the fact that viral resistance was seen at a rate of 10% after a 5 day course ofpleconaril, the implication being that the drug could produce widespread resistance. The question was raised "Will the drug produce cross-resistance to infections that are l4fe- threatening?" Others felt that this type of resistance was unlikely in rhinoviruses.

3. Based on your discussion, does the safety and efficacy profile of pleconaril support its approval for treatment of VRI in adults?

A formal vote was taken and the results were as follows:
No=15 Yes=0

4. If the answer to question 3 is yes, are there any safety or efficacy issues that you would like to see addressed in product labeling? This may include issues in specific sub- populations and/or any risk communication strategies.

This question was not answered due to the results of question #3.

5. If the answer to question 3 is no, please discuss what additional data should be provided to establish pleconaril's safety and efficacy.

The Committee felt that efficacy had been shown, but that the safety data was lacking. They would like to see studies in the following populations: non-white race, pediatrics, elderly, patients with concomitant diseases, patients taking other medications. It was suggested that the food effect needs to be clearly defined (i.e. what kind of snack or meal is required?) It was suggested that the cause of resistance needs to be studied through the characterization ofpatients (i.e. serolype versus point mutation). Studies in the pediatric population and family situations could reveal information on transmission. Some felt that it would be helpful to study repeated exposure (since people tend to get more than one cold per season) and longer durations of exposure (>5 days). More drug interaction studies are needed, with interest placed not necessarily in the mean results but in the outliers, which can serve as signals. The Committee would like to see more information on the interaction with oral contraceptives.

6.Should you agree that the safety and efficacy of pleconaril have been established, please comment on the applicant's proposed phase 4 studies, and provide suggestions for other types of studies (clinical and/or pharmacologic), including designs and patient populations, that should be conducted as phase 4 commitments.

This question was not answered due to the results of question #3.

7. Please discuss any additional suggestions that you have regarding the design of future clinical trials for this indication. Please include in your discussion diagnostic criteria, patient populations, endpoints, and the potential for drug interactions.

Some members stated that f we are looking at symptom relief which was the endpoint in the clinical trials, then it would be interesting to compare pleconaril to available OTC products. Several members expressed interest in obtaining data about the virologic effect of the drug (in addition to the symptomatic effect). There was a discussion about the use of PCR vs. culture diagnostic methods. It was suggested that small formal drug interaction studies be conducted. These drug interaction studies should not be embedded in the clinical trials. Members want to see data in the ITT population vs. ITT infected (the truly infected population) . The fl7' population is representative of real flfe, while the truly infe cted population will show the biological effect of the drug.

The meeting adjourned at 4 p.m.