Antiviral Drugs Advisory Committee
DRAFT MINUTES
November 14, 2002

The Antiviral Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 14, 2002 at the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland. There were approximately 200 people in attendance. The meeting was chaired by Roy M. Gulick, M.D., M.P.H.

The Committee discussed BLA 125061, peginterferon alfa-2a in combination with ribavirin, NDA 21-511, sponsored by Hoffmann-La Roche, Inc., proposed for treatment of chronic hepatitis C. The Committee had received a briefing document from both Hoffmann-La Roche, Inc. and the FDA Division of Clinical Trial Design and Analysis.

The meeting was called to order at 8:30 a.m. by Roy M. Gulick, M.D., M.P.H., Chair. The Committee members, consultants, 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.

Introductory remarks were made by Karen D. Weiss, M.D., Director, Division of Clinical Trial Design and Analysis. Immediately following was a CMC presentation, given by Emanuel F. Petricoin, Ph.D., Division of Therapeutic Proteins.

Hoffmann-La Roche, Inc. gave the following presentation:

Introduction	Dr. Candice Teuber Group Director Regulatory Affairs
Overview of Pegasys-Copegus Development Program	Dr. Joseph Hoffman V.P. & Group Leader Virology and Transplantation
Efficacy	Dr. Frank Duff Clinical Leader
Safety	Dr. Jonathan Solsky Director, Drug Safety and Risk Management
Conclusions	Dr. Joseph Hoffman

The FDA's presentation was given by William Tauber, M.D., Medical Officer, Division of Clinical Trial Design and Analysis.

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

Jules Levin – NATAP
Brian Murphy, M.D., M.P.H. – InterMune, Inc.

The Committee was asked to address the following list of questions:

Questions to the Committee

PEGINTERFERON AND RIBAVIRIN DOSE OPTIMIZATION

The dose of the pegylated interferon (PEGASYS) used in the combination therapy studies, 180 mcg fixed dose administered once weekly SC, was selected based on the monotherapy studies. No dose ranging studies of PEGASYS in combination with ribavirin (COPEGUS) were carried out.

The selection of the ribavirin (COPEGUS) dose was based in part on its similarity to the 'Schering ribavirin' (Rebetol). In study 1 (#15801), the COPEGUS dose was crudely weight adjusted (1000 mg for body weight <75 kg and 1200mg for body weight ≥ 75 kg administered in split dose once daily with food). In study 2 (#15942), two doses of ribavirin were compared, a "low" fixed dose (800 mg) and the "standard" or crudely weight adjusted dose(1000-1200mg).

Exploratory analyses suggested that individuals treated with the combination therapy who were > 85 kg had a lower sustained viral response (SVR) than those < 85 kg, and experienced less toxicity, particularly hematologic toxicity, compared to patients with a lower body weight.

1. Should the sponsor evaluate lower doses (e.g. 135 :g) and/or weight-based dosing (vs. fixed dosing) of PEGASYS in combination with COPEGUS?

   The Committee thought that perhaps a lower dose would be appropriate in patients with genotype 2 or 3 disease or in lower weight patients. However they felt that it would not be acceptable to give a lower dose to patients with genotype 1 disease since it is known to be more resistant. In general the committee expressed a desire to see more analysis of the available data. While lower doses are appealing on the surface (similar efficacy and less toxicity, less cost to pt.) we need to know more. Weight based dosing was not thought to be appropriate due to the variability between patients and the differential response that would likely occur. Additional factors like gender and race should be considered. It was suggested that re-treatment studies might be an optimal place to look for answers

to the dosing questions (i.e. taking resistant patients and trying more intensive regimens with them).

2. Should the sponsor evaluate additional dosages of COPEGUS? If so, please discuss, in light of the dose comparison performed in study #2, what additional doses should be studied.

Note that if licensed, such studies could be performed in the post-marketing period

Some members suggested that a more refined weight adjustment of the ribavirin dose could be used . However, it was noted that dose adjustments are limited by the fact that the drug is only available as a 200mg tablet. Other factors, such as genotype and race, need to be considered.. Again it was suggested that re-treatment trials may be the place to explore dosing questions.

DOSE AND TREATMENT DURATION

In study 2, in addition to the two doses of COPEGUS, two intervals of combination therapy, 24 weeks and 48 weeks, were evaluated. Because of the unequal randomization, with higher risk patients preferentially placed in the higher dose of COPEGUS and longer treatment duration, it is not possible to directly compare total SVRs across all four treatments. Based on comparisons across randomization strata, patients with HCV genotype 1 achieved higher SVRs with the higher COPEGUS dose and longer duration of treatment. For patients with HCV genotype non- 1, neither more COPEGUS nor a longer duration of treatment appear to improve the SVR. However, the SVR data in the small subset of patients infected with HCV genotype 4 suggest a possible benefit for higher COPEGUS dose and longer duration of treatment.

3. If licensed, please discuss what dose of COPEGUS and what duration of treatment should be recommended based on viral factors that predict treatment response. Are there sufficient data in genotype 2 and 3 patients, regardless of viral load, to recommend shorter treatment duration and or 800 mg COPEGUS? If not, what additional studies should be conducted?

4. Should a separate study of patients with genotype 4 be undertaken to determine the optimal dosing regimen? What should be recommended at the present time?

The committee answered questions 3 and 4 together. The committee felt uncomfortable with the designation of genotype 1 vs. genotype non-1 (specifically 2-6) because the data only address genotypes 2&3. They felt that the data strongly support shorter duration of treatment and lower dose of Copegus for genotypes 2&3. Genotype 4 was described as very diverse and large, mostly located in Africa. Patients with genotype 4 have a response rate similar to that of Genotypes 2&3 but they need larger doses. One expert recommended a year of therapy at the higher Copegus dose in patients with genotype 4. Further studies on genotype 4 should be conducted in Africa where there is a large occurrence and an increasing population of HIV/HCV coinfected

patients. For genotype 1 the data support longer duration and higher dose. Results were better in patients with high viral load, however, further refinement of the relationship between viral load vs. response rate is needed.

OUTCOMES BY GEOGRAPHIC REGION

US patients achieved lower SVRs than non-US patients, regardless of treatment arm. For example, in study 1, response rates were in US patients and non-US patients were 42% and 61%, respectively. The US patients had a greater preponderance of higher risk factors, including genotype 1, cirrhosis, older age, and higher body weight. In the multivariate analysis, these factors had more of an impact on ultimate treatment response, while geographic region contributed less.

Assuming the differences across regions are real, regardless of causative factors, studies conducted predominantly in the US will yield lower SVRs than studies conducted predominantly outside the US.

The overall reported incidence of adverse events per patient was higher in US patients compared to non-US patients.

5. Please discuss the implications of these geographical differences; in particular, the implications if cross study comparisons are attempted. What additional factors (other than stated above) might help explain these differences?

   Some members felt that there are no geographical differences of note and that genotype is the driving factor. Others felt that the data points show that there are geographic differences. The committee came to the question "Is geography a predictor?" It was recommended that more analysis of the cofactors needs to be explored.

PATIENTS WITH CIRRHOSIS

Of the three efficacy studies conducted in the PEGASYS monotherapy program, one specifically targeted patients with cirrhosis. Approximately 80% of the patients in that study had cirrhosis or bridging fibrosis. In contrast, approximately 20% of patients enrolled in the other two trials had cirrhosis, a percentage more representative of studies in chronic hepatitis C. The monotherapy label specifically identifies the cirrhotic population as one in which efficacy had been demonstrated.

In the PEGASYS/COPEGUS combination studies, patients with cirrhosis comprised 13 and 25% of the patients.

6. Please discuss the implications of cirrhosis. Should clinical development programs for products intended for treatment of patients with chronic hepatitis C infection include separate studies for patients with cirrhosis? Should presence of cirrhosis be a stratification variable?

Some members suggested that in cirrhosis the response rate might be less, however, that is not a reason to alter the treatment regimen. One expert stated that cirrhosis is a predictor but not an effect modifier. Separate studies for cirrhotics are not necessary if large studies with stratification are done. The valuable data include response rate, relapse rate, and safety information.

RECOMMENDATIONS FOR DISCONTINUATION OF TREATMENT FOR INADEQUATE EARLY VIRAL RESPONSE

In both studies, study subjects who did not demonstrate either an early virologic response (HCV negative or ≥ 2 $\log_{10}$ decrease) or an early biochemical response (normal ALT) *could* be withdrawn from the study by 12 weeks of therapy and were to be withdrawn from study if unresponsiveness persisted by 24 weeks. Ninety-six percent of patients who showed no early virologic response by week 12 failed to achieve a SVR.

7. Please discuss what advice should be provided regarding early discontinuation of treatment for lack of efficacy.

The committee provided a variety of responses. The full discussion is available in the verbatim transcript of the meeting.

ADVERSE EVENTS

Compared to Interferon combination therapy, Peginterferon combination therapy was associated with a higher incidence of serious adverse events (12% vs. 9%) including serious infections (4% vs 2%) and a higher incidence of grade 4 neutropenia (5% vs 1%) and grade 3 thrombocytopenia (5% vs. 0.2%). There is the suggestion that some patients had a blunted ability to respond to infections. PEGASYS combination treatment resulted in a high incidence of reversible lymphopenia. Interferon treatment in general appears to result in higher triglyceride levels, but this parameter was not rigorously assessed in clinical studies.

8. Please discuss how best to further evaluate, characterize, and minimize the toxicity of PEGASYS/COPEGUS, specifically with regard to the hematologic and infectious events. Note that some of these assessments could be incorporated into the design of ongoing studies conducted in other clinical settings.

The committee felt most concerned with the serious infections. It was suggested that a prospective monitoring system be established to assess infection rates. There was a difference of opinion as to how to manage hematologic effects (i.e. dose modification vs. growth factor administration).

It was suggested that subset analyses be done to assess the risk/benefit of adverse events at different doses.

OVERALL SAFETY AND EFFICACY

9. Do these data demonstrate the safety and efficacy of PEGASYS/COPEGUS for the treatment of patients with chronic hepatitis C infection?

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

   Yes = 12 No=0 Abstentions=0

The meeting adjourned at 4 p.m.