CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-511

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

DATE: November 27, 2002

TO: NDA 21-511 (COPEGUS™, ribavirin tablets)

FROM: Russell Fleischer, PA-C, MPH
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THROUGH: Steve Gitterman, MD (eso 11/27/02)
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RE: Medical Review of NDA

Background

The applicant, Roche Pharmaceuticals, submitted NDA 21-511 to seek approval of Copegus™ Tablets for use in combination with Pegasys® (peginterferon alfa-2a, recombinant, currently approved as monotherapy) for the treatment of adults with chronic hepatitis C virus (HCV) infection. A companion BLA to add combination use to the Pegasys labeling (125061-0) was submitted to CBER. The application contained safety and efficacy data from two clinical trials in which approximately 2000 patients received the combination of Copegus (800, 1000 and 1200 mg) and Pegasys (180 µg/week) for 24 or 48 weeks.

Ribavirin has been available in a capsule formulation (Rebetol® Capsules, Schering Corporation) for use with Intron® A (1998) or Peg-Intron® (2001) for treatment of chronic HCV infection. Although the active ingredient in Copegus Tablets is ribavirin, it was developed as a new drug under section 505(b)1, and underwent comprehensive preclinical and clinical testing. A clinical pharmacology study demonstrated that the Copegus is bioequivalent to Rebetol.

Because ribavirin has had extensive prior use in the treatment of HCV infection, there is a significant body of knowledge about the toxicities of ribavirin. Further, because the ribavirin in Copegus is bioequivalent to the ribavirin in Rebetol, toxicities were expected to be similar to those seen in earlier studies of interferon/ribavirin combinations.

Clinical Trial Database and Efficacy Outcomes

The applicant conducted two studies to establish the clinical efficacy and safety of Copegus when coadministerd with Pegasys in adults with chronic HCV infection. CBER was assigned the review of the Clinical/Statistical portions of the application. Please see Dr. William Tauber's review of BLA 125061-0 for a comprehensive discussion of safety and efficacy. Only a brief overview of CBER's findings is presented herein.

In Study NV15801, patients were randomized to receive either Pegasys 180 µg once weekly (qw) with an oral placebo, Pegasys 180 µg qw with Copegus 1000 mg orally (body weight <75 kg) or 1200 mg (body weight ≥75 kg) or interferon alfa-2b (Intron A) 3 MIU sc tiw plus ribavirin (Rebetol) 1000-1200 mg. All patients received 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. Sustained virologic response rates (defined as undetectable HCV RNA at the end of the 24 week treatment free follow-up period) were 28%, 50%, and 42%, in the Pegasys monotherapy, Pegasys plus Copegus, and interferon plus ribavirin arms, respectively. In conclusion, this study clearly demonstrated that the addition of ribavirin, as either Copegus or Rebetol, produced an expected and substantial increase in sustained response rates compared to Pegasys monotherapy.

In study 15942, all patients received Pegasys 180 µg sc qw and were randomized to:

- Copegus 800 mg or 1000 mg (<75 kg) or 1200 mg (≥75 kg) for 24 weeks.
- Copegus 800 mg or 1000 mg (<75 kg) or 1200 mg (≥75 kg) for 48 weeks.

Assignment to the four treatment arms was stratified by viral genotype and baseline HCV viral titer. Patients with genotype 1 and high viral titer (defined as $>2x10^6$ HCV RNA copies/ml serum) were preferentially assigned to treatment for 48 weeks. The sustained virologic response response rates (defined as undetectable HCV RNA at the end of the 24-week treatment free follow-up period) are presented in Table 1.

Table 1. Sustained Virologic Response Rates, Study NV15942.

	24 Weeks Treatment		48 Weeks Treatment	
	Pegasys+Copegus 800 mg (N=207)	Pegasys+Copegus 1000mg or 1200 mg (N=280)	Pegasys+Copegus 800 mg (N=361)	Pegasys+Copegus 1000mg or 1200 mg (N=436)
Genotype 1	29/101 (29%)	48/118 (41%)	97/250 (39%)	136/271 (50%)
Genotype non-1	83/106 (78%)	129/162 (80%)	83/111 (75%)	123/165 (75%)

This study demonstrated that, irrespective of baseline viral load, patients with genotype 1 virus achieve higher sustained response rates when administered 48 weeks of combination treatment. In contrast, 24 weeks appears to be sufficient to produce high sustained response rates in patients with genotypes 2 and 3 as there was no significant improvement in treatment outcomes associated with an additional 24 weeks of treatment.

Summary of Important Ribavirin-Related Safety Findings

- **Hemolytic Anemia**

The most important clinical toxicity of ribavirin is hemolytic anemia. Overall, 22% of patients experienced reductions in their hemoglobin to levels that required modifications of their ribavirin dose. Significant anemia (hemoglobin <10 g/dL) was observed in 13% of patients. Ribavirin

induced anemia occurs within 1 to 2 weeks of initiation of therapy, and generally reverses upon cessation of treatment.

Serious cardiovascular events, including myocardial ischemia and angina, were reported in patients with anemia in the pivotal studies. Therefore, it will be recommended that patients be assessed for underlying cardiac disease before initiation of Copegus therapy, and that patients with pre-existing cardiac disease have electrocardiograms administered before treatment and be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, COPEGUS should be suspended or discontinued.

The labeling will carry Warnings related to the monitoring and management of ribavirin-induced anemia. Specifically, clinicians and patients will be informed that because the initial drop in hemoglobin may be significant, hemoglobin or hematocrit levels should be obtained pretreatment and at weeks 2 and 4, or more frequently if clinically indicated, and that patients be followed as clinically appropriate.

- **Teratogenicity and Risk to the Fetus**

It is well documented that ribavirin produces embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. And survival of fetuses and offspring was reduced. It is not known whether ribavirin is contained in sperm and, if so, could exert a potential teratogenic effect upon fertilization of the ova. The applicant conducted a battery of pre-clinical toxicology studies and found that its formulation of ribavirin produced the same results as seen for other ribavirin products.

Therefore, Copegus should not be used by pregnant women or by men whose female partners are pregnant. Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive Copegus unless the patient and his/her partner are using effective contraception (two reliable forms) during therapy and, because of the long half-life of ribavirin, for 6 months posttherapy. To monitor maternal-fetal outcomes of pregnant women exposed to Copegus, a Copegus Pregnancy Registry has been established.

Recommendation

CBER determined that Copegus Tablets when used with Pegasys was safe and effective for the treatment of chronic HCV infection in adults. This medical reviewer concurs with CBER's conclusions, and recommends that NDA 21-511 be approved.