CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW SUMMARY

NDA, BLA:	NDA 21511/S-023 and BLA 103964/5213
Submission Dates:	02/18/2011
Brand Name	Copegus® and Pegasys®
Generic Name:	Ribavirin and interferon alfa-2a
Formulation:	200 mg Tablet (Copegus) and 180 μg/1.0 mL Vial for single use and180 μg/0.5 mL Prefilled Syringe for single use (Pegasys)
Applicant:	Hoffmann-La Roche
Reviewer:	Jenny H. Zheng, Ph.D.
Team Leader:	Sarah Robertson, Pharm.D.
OCP Division:	DCP 4
Clinical Division:	DAVP
Indication:	Chronic hepatitis C virus

Summary:

Pegasys® is currently indicated for use alone or in combination with ribavirin (Copegus®) for the treatment of chronic hepatitis C in adult patients with compensated liver disease who have not been previously treated with interferon alpha. Combination therapy with Copegus® is recommended unless a patient has a contraindication or significant intolerance to ribavirin. The approved Pegasys® dose is 180 μg once weekly for 24 weeks or 48 weeks depending on genotype, the status of coinfection with HIV, or if used with ribavirin. The approved Copegus® adult doses are 800 to 1200 mg/day (divided in two doses) based on patient's body weight or genotype.

The Office of Clinical Pharmacology has reviewed the information submitted to BLA103949 and NDA21511. The information provided in this BLA/NDA were adequate to support the proposed body surface area (BSA) based dosing of Pegasys® (180 μg/1.73m^2 x BSA once weekly subcutaneously, to a maximum dose of 180 μg) in combination with the body weight based Copegus® (15 mg/kg/day divided in two doses administered orally) in pediatric patients at least 5 years old with chronic hepatitis C. The dose of 15 mg/kg/day is currently approved for Rebetol® (ribavirin manufactured by Schering Plough) in pediatric patients 3 years of age and older.

Both 100 mg and 200 mg strength ribavirin tablets were used in Study NV17424, the clinical study conducted in pediatric patients in support of this supplement. However, the Applicant is not planning to market the 100 mg tablet. Because no suitable pediatric formulation is proposed at this time, Copegus® doses are rounded to the nearest 200 mg, based on the available adult strength tablet. Table 1 shows the proposed Copegus® daily doses. Copegus daily doses are divided into AM and PM doses.

Table 1: Proposed Copegus Doses in pediatric patients at least 5 years of age

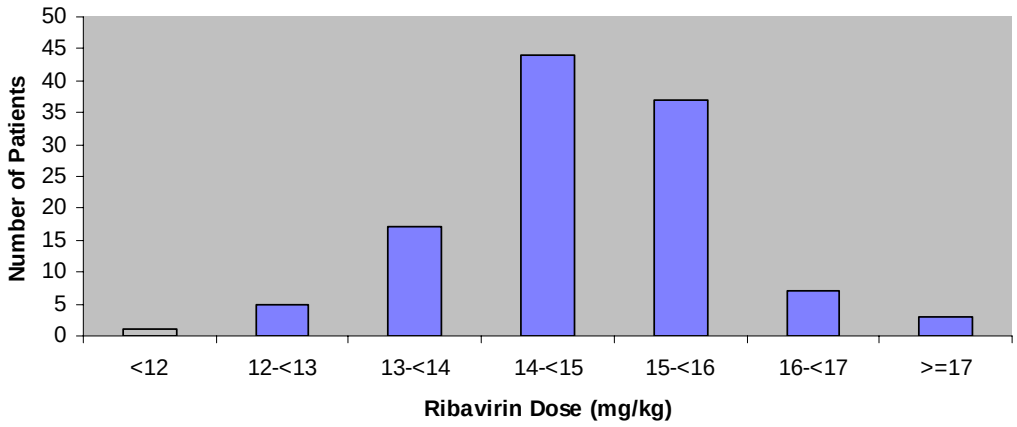
Body weight (kg)	Daily Dose (mg)	Range of dose (mg/kg/day)		Copegus Number of Tablets
23 – 33	400	12.1	17.4	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
34 – 46	600	13.0	17.6	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
47 – 59	800	13.6	17.0	2 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
60 – 74	1000	13.5	16.7	2 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.
≥75	1200	≤16.0		3 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.

For patients with body weight < 75 kg, Copegus® doses range from 12.1 mg/kg/day to 17.6 mg/kg/day. This range is within the dose range studied in NV17424, when doses were rounded to the nearest 100 mg (12.0 to 18.0 mg/kg/day, Table 2). Figure 1 shows that most enrolled patients were dosed with 14 to 16 mg/kg. (b) (4)

Table 2: Copegus Doses studied in NV17424

Body weight (kg)	Daily Dose (mg) (divided in 2 doses)	Range of dose (mg/kg/day)	
13.5 - 16.6	200	14.8	12.0
16.7 - 23.3	300	18.0	12.9
23.4 - 29.9	400	17.1	20.1
30.0 - 36.6	500	16.7	13.7
36.7 - 43.3	600	16.3	13.9
43.4 - 49.9	700	16.1	14.0
50.0 - 56.6	800	16.0	14.1
63.4 - 69.9	1000	15.8	14.4
70.0 - 76.6	1100	15.8	14.4
≥ 76.7	1200	≤15.6	

Figure 1: Ribavirin Dose distribution in Study NV17424



Study NV17424 is a safety and efficacy study of PEG-IFN alfa-2a in combination with ribavirin versus PEG-IFN alfa-2a alone for the treatment of chronic hepatitis C virus (HCV) in children aged 5 to 17 years of age. One hundred and fourteen (114) subjects were initially randomized to PEG-IFN alfa-2a plus ribavirin (n=55) and PEG-IFN alfa-2a monotherapy (n=59) groups. PEG-IFN alfa-2a was administered at 180 μg/1.73 m^2 subcutaneously. Ribavirin dose is shown in Table 2. Between weeks 24 and 28 continuation of treatment was determined as follows. Patients with undetectable HCV RNA (< 50 IU/mL), as measured by the COBAS AMPLICOR HCV Test, v2.0, were considered virologic responders and were to continue treatment until week 48 without change to their regimen. Patients with detectable HCV RNA at week 24 were considered nonresponders. Virologic nonresponders either discontinued treatment (if they had initially received ribavirin) or were to continue to receive PEG-IFN alfa-2a plus the addition of ribavirin (if they had initially received placebo) until week 56 as part of the "compassionate" combination treatment arm. This "compassionate" combination treatment was to be continued for 24 weeks beyond week 52 if the patient had responded and the virus was undetectable at week 52. All subjects were followed for 24 weeks post-treatment. No pharmacokinetics was evaluated in the study.

In Study NV17424, if severe adverse reactions or laboratory abnormalities developed during combination PEGASYS/COPEGUS therapy, the dose was modified until the adverse reactions abated. If intolerance persisted after dose adjustment, PEGASYS/COPEGUS therapy was discontinued. The rules for dose reduction were applied uniformly at all participating centers. The following downward dose adjustments for PEG-IFN alfa-2a were recommended in the protocol:
• One level adjustment: to 135 μg x BSA / 1.73 m^2
• Two level adjustment: to 90 μg x BSA / 1.73 m^2
• Three level adjustment: to 45 μg x BSA / 1.73 m^2

In Study NV17424, the recommended downward dose adjustment for ribavirin was from 15 mg/kg/day to 7.5 mg/kg/day.

The proposed reduction for PEG-IFN is the same as the dose reduction applied in Study NV17424. The proposed reduction scheme for Copegus in pediatrics is shown in Table 3. The dose reduction scheme for Copegus is reasonable.

Table 3: Dose Reduction Scheme for COPEGUS in Pediatrics

Body weight kg (lbs)	Original Dose	One Step Dose Modification	Range of dose (mg/kg/day)		**COPEGUS** Number of Tablets
23 – 33 (51-74)	400 mg/day	200 mg/day	6.1	8.7	1 x 200 mg tablets A.M.
34 – 46 (75-102)	600 mg/day	400 mg/day	8.7	11.8	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
47 – 59 (103-131)	800 mg/day	400 mg/day	6.8	8.5	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
60 – 74 (132-164)	1000 mg/day	600 mg/day	8.1	10	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
≥75 (>165)	1200 mg/day	600 mg/day	≤8.0		1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.

In Study NV17424, for pediatric subjects treated for 48 weeks with PEGASYS in combination with ribavirin, 53% (29/55) achieved an SVR as compared to 20% (12/59) SVR rate in the PEGASYS monotherapy arm. In this study, 82% of pediatric subjects were infected with HCV Genotype 1. The SVR rate for combination therapy in this study was similar to what have been observed in adults.

The study showed the adverse event profile in pediatric subjects was similar to that observed in adults. Growth inhibition was observed in pediatric subjects. During combination therapy for up to 48 weeks with PEGASYS and COPEGUS, negative changes in weight for age z-score and length for age z-score after 48 weeks of therapy compared with baseline were observed. Likewise, percentiles of the normative population for subject weight and height decreased during treatment. At the end of 2 years after treatment, all patients were near or above the normative growth curve percentiles for weight and height

PEG-IFN alfa-2a pharmacokinetics were studied in pediatric subjects in Study NR16141. This is a Pegasys pharmacokinetics study following multiple-dose administration in young children with chronic hepatitis C infection. In this study, 14 subjects were studied (2 to 8 years of age); there were 5 subjects who were between 6 to 8 years of age, and other subjects were within 2-4 years of age. Sparse samples (predose, 24, 96, and 168 hours after the first dose and Week 24 dose, and predose at Weeks 4, 8, and 12) were collected in all subjects. The applicant has developed a population PK analysis to simulate the PK for patients from 2 to 17 years of age. However, there is insufficient pharmacokinetic data to determine the pharmacokinetics of pediatrics across the entire proposed population (5 to 17 years old). Therefore, the results of Study NR16141 were not used for determination of PEG-IFN alfa-2a dose and will not be reviewed in this review cycle. The applicant was requested to include the PEG-IFN alfa-2a PK data from their pediatric hepatitis B study to support the pharmacokinetic model. In addition, no ribavirin PK was determined in pediatrics dosed with Copegus. However, the doses that are proposed, which approximate the doses studied in NV17424, as indicated in Table 1, are recommended, pending on the Medical Officer's review of efficacy and safety.

Signature:

Primary Reviewer: Jenny Zheng

Team leader: Sarah Robertson

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/s/

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07/18/2011

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