PACK INSERT FOR MALAYSIA

Copegus ®

Ribavirin

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Direct acting antiviral

1.2 Type of Dosage Form

Supplied as a 200mg film-coated tablet for oral administration.

COPEGUS film-coated tablets are light pink to pink flat oval tablets containing 200 mg of ribavirin. The tablets are engraved "ROCHE" on one side and "RIB 200" on the other side.

1.3 Route of Administration

oral

1.4 Qualitative and Quantitative Composition

Active ingredient: ribavirin

Each 200 mg film-coated tablet contains 200 mg of ribavirin.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indications

Copegus is indicated, in combination with peginterferon alfa-2a or interferon alfa-2a for the treatment of chronic hepatitis C in previously untreated adult patients and who are positive for serum HCV RNA, including patients with compensated cirrhosis.

Copegus in combination with peginterferon alfa-2a is also indicated for the treatment of patients who have failed previous treatment with interferon alpha (pegylated or non-pegylated) alone or in combination therapy with ribavarin. Demonstrated efficacy included HCV patients co-infected with clinically stable HIV.

Please refer to the label of peginterferon alfa-2a or interferon alfa-2a products for additional information.

2.2 Dosage and Method of Administration

Copegus is used in combination with peginterferon alfa-2a or interferon alfa-2a. The exact dose and duration of treatment depend on the interferon product used.

Please refer to the label of peginterferon alfa-2a or interferon alfa-2a for further information on dosage and the duration of treatment when Copegus is given in combination with either of these products.

In combination with Pegasys (peginterferon alfa-2a)

The daily dose and duration of Copegus given in combination with Pegasys should be individualized based on the patient's viral genotype and body weight (see Table 1). The daily dose of Copegus is to be administered orally in two divided doses (morning and evening) with food.

Chronic Hepatitis C

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 regardless of pre-treatment viral load should receive 48 weeks of therapy. Treatment for 24 weeks may be considered in patients infected with genotype 1 with low viral load (LVL) (≤ 800,000 IU/mL) at baseline or genotype 4 who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration. In these patients, tolerability to combination therapy and additional prognostic factors such as degree of fibrosis should be taken into account when deciding on treatment duration. Shortening the treatment duration in patients with genotype 1 and high viral load (HVL) (>800, 000 IU/ml) at baseline who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24 should be considered with even more caution since the limited data available suggest that this may significantly negatively impact the sustained virologic response (see Table 1 and section 3.1.2).

Patients infected with HCV genotype 2 or 3 who have detectable HCV RNA at week 4, regardless of pre-treatment viral load should receive 24 weeks of therapy. Treatment for 16 weeks may be considered in selected patients infected with genotype 2 or 3 with LVL at baseline who become HCV negative by week 4 of treatment. Overall 16 weeks of treatment may be associated with a higher risk of relapse than a 24 week treatment duration (see section 3.1.2). In these patients, tolerability to combination therapy and the presence of additional clinical or prognostic factors such as degree of fibrosis should be taken into account when considering deviations from standard treatment duration. Shortening the treatment duration in patients infected with genotype 2 or 3 with HVL at baseline who become HCV negative by week 4 should be considered with more caution as this may significantly negatively impact the sustained virological response (see section 3.1.2).

Available data for patients infected with genotype 5 or 6 are limited; therefore combination treatment with 1000/1200 mg of ribavirin for 48 weeks is recommended.

Table 1 Copegus Dosing Recommendations in Combination with Peginterferon alfa-2a for HCV Patients

Genotype	Daily Copegus Dose	Duration of treatment	Number of 200 mg Tablets
Genotype 1 LVL with RVR*	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks	5 (2 morning; 3 evening) 6 (3 morning; 3 evening)
Genotype 1 HVL with RVR*	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks	5 (2 morning; 3 evening) 6 (3 morning; 3 evening)
Genotype 4 with RVR*	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks	5 (2 morning; 3 evening) 6 (3 morning; 3 evening)
Genotype 1 or 4 without RVR*	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks	5 (2 morning; 3 evening) 6 (3 morning; 3 evening)
Genotype 2 or 3 LVL with RVR**	800 mg (regardless of weight)	16 weeks or 24 weeks	4 (2 morning; 2 evening)
Genotype 2 or 3 HVL with RVR**	800 mg (regardless of weight)	24 weeks	4 (2 morning; 2 evening)
Genotype 2,3 without RVR**	800 mg (regardless of weight)	24 weeks	4 (2 morning; 2 evening)

*RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24;

**RVR = rapid viral response (HCV RNA negative) by week 4

LVL= ≤ 800,000 IU/mL; HVL= > 800,000 IU/mL

Chronic Hepatitis C prior treatment failures

The recommended dosage of Copegus, in combination with 180 mcg of peginterferon alfa-2a, is 1000 mg or 1200 mg for patients < 75 kg and ≥ 75 kg respectively, regardless of genotype. Copegus should be administered with food. The recommended duration of therapy is 72 weeks in genotype 1 or 4 patients and 48 weeks in genotype 2 or 3 patients.

HIV-HCV Co-infection

The recommended dosage of Copegus, in combination with 180 mcg of peginterferon alfa-2a is 800 mg of ribavarin daily for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with Copegus doses greater than 800 mg daily or a duration of therapy less than 48 weeks has not been studied.

Predictability of response

Naïve patients

Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see Table 2).

Table 2. Predictive Value of Week 12 Virological Response at the Recommended Dosing Regimen while receiving Copegus and Pegasys Combination Therapy in HCV Patients

Genotype	Negative			Positive		
	No response by week 12	No sustained response	Predictive Value	Response by Week 12	Sustained response	Predictive Value
Genotype 1 (N=569)	102	97	95% (97/102)	467	271	58% (271/467)
Genotype 2 and 3 (N=96)	3	3	100% (3/3)	93	81	87% (81/93)

A similar negative predictive value of early virological response by week 12 has been observed in HIV-HCV co-infected patients treated with peginterferon alfa-2a monotherapy or in combination with Copegus (100% (130/130) or 98% (83/85), respectively). Positive predictive values of 45% (50/110) and 70% (59/84) were observed, respectively, for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Prior non-responder patients

In non-responder patients retreated for 48 (genotype 2 and 3) or 72 weeks (genotype 1 and 4), viral suppression at week 12 (undetectable HCV RNA defined as HCV RNA <50 IU/mL) has shown to be predictive for sustained virological response. The negative predictive value of viral suppression at week 12 for 48 and 72 weeks of treatment is 96% (363/380) and 96% (324/339), respectively. The positive predictive value for 48 and 72 weeks of treatment is 35% (20/57) and 57% (57/100), respectively.

Discontinuation of treatment

Discontinuation of treatment is recommended if at least a 2 log10 reduction from baseline or undetectable HCV RNA has not been demonstrated by 12 weeks of therapy (see section Predictability of response). Additionally, if patients have not achieved undetectable HCV RNA by week 24, therapy should be discontinued.

In combination with Roferon-A (interferon alfa-2a)

Dose to be administered:

The recommended dose of Copegus in combination with interferon alfa-2a solution for injection depends on the patient's body weight (see Table 3).

Duration of treatment

Patients should be treated with combination therapy with interferon alfa-2a for at least six months. Patients with HCV genotype 1 infections should receive 48 weeks of combination therapy. In patients infected with HCV of other genotypes, the decision to extend therapy to 48 weeks should be based on other prognostic factors (such as high viral load at baseline, male gender, age >40 years and evidence of bridging fibrosis).

Table 3. Copegus Dosing Recommendations in Combination with Interferon alfa-2a for HCV Patients

Patient weight (kg)	Daily Copegus dose	Duration of treatment	Number of 200 mg tablets
<75	1000 mg	24 or 48 weeks	5 (2 morning, 3 evening)
≥75	1200 mg	24 or 48 weeks	6 (3 morning, 3 evening)

2.2.1 Special Dosage Instructions

Dosage modification for adverse reactions

Please refer to the package insert of peginterferon alfa-2a or interferon alfa-2a for further information on dose adjustment and discontinuation of treatment for either of these products.

If severe adverse reactions or laboratory abnormalities develop during therapy with Copegus and peginterferon alfa-2a or interferon alfa-2a, modify the dosages of each product until the adverse reactions abate. If intolerance persists after Copegus dose adjustment, discontinuation of the drug may be necessary.

For management of treatment-emergent anemia, the following guidelines were developed in the clinical trials (see Table 4).

Table 4. Copegus Dosage Modification Guidelines for Management of Treatment-Emergent Anemia

Laboratory Values	Reduce Copegus dose to 600 mg/day* only if:	Discontinue Copegus if**:
Hemoglobin: Patients with no cardiac disease	<10 g/dl	<8.5 g/dl
Hemoglobin: Patients with History of Stable cardiac disease	>2 g/dl decrease in hemoglobin during any 4 week period during treatment (permanent dose reduction)	<12 g/dl after 4 weeks of dose reduction

* Patients whose dose of Copegus is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets in the evening.

** If the abnormality is reversed, Copegus may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to higher doses is not recommended.

Use in renal impairment

Standard dose regimens (adjusted by the body weight cutoff of 75 kg) of ribavirin result in substantially higher plasma concentrations of ribavirin in patients with renal impairment compared to patients with normal renal function, resulting in increased incidence of anemia and frequent dose reductions. Thus, the total daily dose of Copegus should be reduced for patients of chronic hepatitis C infection having creatinine clearance less than or equal to 50 ml/min as shown in Table 5.

Table 5 Dosage Modification for Renal Impairment

Creatinine Clearance	Copegus Dose (daily)
30 to 50 ml/min	Alternating doses, 200 mg and 400 mg every other day
Less than 30 ml/min	200 mg daily
Hemodialysis	200 mg daily

The dose of Copegus should not be further modified in patients with renal impairment. If severe adverse reactions or laboratory abnormalities develop, Copegus should be interrupted, if appropriate, until the adverse reactions resolve or decrease in severity. If intolerance reoccurs or worsens after restarting Copegus, therapy should be discontinued. Currently there is no safety or efficacy data available about the use of Copegus in pediatric subjects with renal impairment.

2.3 Contraindications

Copegus is contraindicated in patients with hypersensitivity to ribavirin or to any of the excipients.

Copegus must not be used by women who are pregnant or by men whose female partners are pregnant.

Copegus is contraindicated in patients with hemoglobinopathies (e.g., thalassemia, sickle-cell anemia)

Pegasys and Copegus combination therapy is contraindicated in patients with hepatic decompensation.

Initiation of Pegasys contraindicated in HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6, except if only due to indirect hyperbilirubinemia caused by drugs such as atazanavir and indinavir (Please refer to Pegasys Prescribing Information for Child Pugh assessment).

Please refer to the label of peginterferon alfa-2a or interferon alfa-2a products for additional information.

2.4 Warnings and Precautions

2.4.1 General

Based on results of clinical trials, the use of ribavirin as monotherapy is not effective and Copegus must not be used alone.

Copegus used in combination therapy should be administered under the guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of further therapy.

Teratogenic risk: Prior to initiation of treatment with Copegus the physician must comprehensively inform the patient of the teratogenic risk of ribavirin, the necessity of effective and continuous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during treatment with ribavirin (see section 2.5.1).

Acute hypersensitivity: If an acute hypersensitivity reaction (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) develops, Copegus must be discontinued immediately and appropriate medical therapy instituted. Transient rashes do not necessitate interruption of treatment.

Hemolysis and Cardiovascular system: If there is any deterioration of hemoglobin blood concentration, Copegus should be suspended or discontinued (see section 2.2., Table 1). Although ribavirin has no direct cardiovascular effects, anemia associated with Copegus may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, Copegus must be administered with caution to patients with pre-existing significant or unstable disease. Cardiac status must be assessed before initiation of therapy and monitored clinically during therapy. If there is any deterioration of cardiovascular status, ribavirin therapy should be stopped (see section 2.2, Table 3). It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to and during the course of treatment.

The use of Copegus with peginterferon alfa-2a combination therapy in chronic hepatitis C patients who have failed prior treatment, has not been adequately studied in patients who discontinued prior therapy for haematological adverse events. Physicians considering treatment in these patients should carefully weigh the risks versus the benefits of retreatment.

Pancytopenia (marked decreases in red blood cells, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of ribavirin and azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see section 2.4.5).

Organ transplant recipients: The safety and efficacy of Pegasys and Copegus treatment have not been established in patients with liver and other transplantations. As with other alpha interferons, liver and renal graft rejections have been reported on Pegasys, alone or in combination with Copegus.

Hepatic function: In patients who develop evidence of hepatic decompensation during treatment, Copegus in combination with peginterferon alfa-2a or interferon alfa-2a should be discontinued.

Renal Impairment: The pharmacokinetics of ribavirin is altered in patients with renal dysfunction due to reduction of apparent clearance in these patients (see section 2.5.5 and 3.2.5). It is recommended that renal function be evaluated in all patients prior to initiation of Copegus. Based on pharmacokinetic modelling and simulation, dose adjustments are recommended in patients with significant renal impairment (see section 2.2.1).

Patients with creatinine clearance less than or equal to 50 mL/min receiving Copegus should be carefully monitored.

Laboratory tests

Standard hematologic tests and blood chemistries (complete blood count [CBC] and differential, platelet count, electrolytes, serum creatinine, liver function tests, uric acid) must be conducted in all patients prior to initiating therapy. After initiation of Copegus therapy, laboratory evaluations should be performed at 2 and 4 weeks of therapy and periodically thereafter as clinically appropriate. Acceptable baseline values that may be considered as a guideline prior to initiation of Copegus in combination with peginterferon alfa-2a or interferon alfa-2a are:

- Hemoglobin ≥ 12 g/dl (female); ≥ 13 g/dl (male)
- Platelets ≥ 90,000/mm³
- Neutrophil Count ≥ 1,500/mm³
- For HIV-HCV co-infected patients: CD4+ ≥ 200/µl or CD4+ ≥ 100/µl - < 200/µl and HIV-1 RNA < 5000 copies/mL using Amplicor HIV-1 Monitor Test, v 1.5.

For women of childbearing potential: Female patients must have a routine pregnancy test performed monthly during treatment and for 6 months thereafter. Female partners of male patients must have a routine pregnancy test performed monthly during treatment and for 6 months thereafter.

Please refer to the label of peginterferon alfa-2a or interferon alfa-2a products for additional information.

2.4.2 Ability to Drive and Use Machines

Copegus has no or negligible influence on the ability to drive or operating machinery; however, interferon alfa-2a or peginterferon alfa-2a used in combination may have an effect. Thus, patients who develop fatigue, somnolence, or confusion during treatment must be cautioned to avoid driving or operating machinery.

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction

Interaction studies have been conducted with ribavirin in combination with peginterferon alfa-2a, interferon alfa-2b and antacids. Ribavirin concentrations are similar when given as monotherapy or in combination with peginterferon alfa-2a or interferon alfa-2b.

Any potential for interactions may persist for up to 2 months (5 half-lives for ribavirin) after cessation of Copegus therapy due to the long half-life.

Results of in-vitro studies using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme-mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that ribavirin induces liver enzymes. Therefore, there is a minimal potential for P450 enzyme-based interactions.

Antacid: The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid containing magnesium, aluminium and methicone; AUC_{tf} decreased 14%. It is possible that the decreased bioavailability in this study was due to delayed transit of ribavirin or modified pH. This interaction is not considered to be clinically relevant.

Nucleoside analogs: Ribavirin was shown *in-vitro* to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these findings is unknown. However, these *in-vitro* findings raise the possibility that concurrent use of Copegus with either zidovudine or stavudine might lead to increased HIV plasma viremia. Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with Copegus concurrently with either of these two agents. If HIV RNA levels increase, the use of Copegus concomitantly with reverse transcriptase inhibitors must be reviewed.

From a 12 week pharmacokinetic substudy examining the effects of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine, zidovudine or stavudine), there was no evidence of drug interaction observed in 47 HIV-HCV co-infected patients. Plasma exposure to ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).

Didanosine (ddI): Ribavirin potentiated the antiretroviral effect of didanosine (ddI) *in-vitro* and in animals by increasing the formation of the active triphosphate anabolite (ddATP). This observation also raised the possibility that concomitant administration of ribavirin and ddI might increase the risk of adverse reactions related to ddI (such as peripheral neuropathy, pancreatitis, and hepatic steatosis with lactic acidosis). While the clinical significance of these findings is unknown, one study of concomitant ribavirin and ddI in patients with HIV disease did not result in further reductions in viremia or an increase in adverse reactions. Plasma pharmacokinetics of ddI were not significantly affected by concomitant ribavirin in this study, although intracellular ddATP was not measured.

Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased

when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactemia/lactic acidosis have been reported with use of ribavirin.

Azathioprine: Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine.

In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close hematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped (see section 2.4.1).

2.5 Use in Special Population

2.5.1 Pregnancy

Copegus must not be used by women who are pregnant or by men whose female partners are pregnant.

Evaluation of experimental animal studies showed reproductive toxicity. Significant teratogenic and/or embryocidal potential have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses well below the recommended human dose. 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 ribavirin dose. Survival of fetuses and offspring was reduced.

Extreme care must be taken to avoid pregnancy in female patients. Copegus therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within 6 months from stopping treatment the patient must be advised of the significant teratogenic risk of ribavirin to the fetus.

Male patients and their female partners: Extreme care must be taken to avoid pregnancy in partners of male patients taking Copegus. Ribavirin accumulates intracellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Therefore, men must be instructed to use a condom to minimise delivery of ribavirin to their partners. Male patients and their female partners of childbearing age must be counselled to use 2 forms of effective contraception during treatment with Copegus and for 6 months after treatment has been concluded. Women must have a negative pregnancy test before therapy is started.

2.5.2 Nursing Mothers

It is not known whether Copegus is excreted in human milk. Because of the potential for adverse reactions in nursing infants, a decision should be made either to discontinue nursing or not to initiate therapy.

2.5.3 Pediatric Use

Safety and effectiveness of ribavirin in combination with peginterferon alfa-2a and interferon alfa 2-a in these patients have not been evaluated. Treatment with Copegus is not recommended for use in children and adolescent under age of 18.

2.5.4 Geriatric Use

There does not appear to be significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to administration of Copegus.

2.5.5 Renal Impairment

The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients (see Section 3.2). Therefore it is recommended that the renal function be evaluated in all patients prior to initiation of Copegus, preferably by estimating the patient's creatinine clearance. Patients with moderate or severe renal impairment (creatinine clearance ≤50 mL/min) not receiving chronic hemodialysis did not tolerate 600 mg and 400 mg daily doses of Copegus, respectively and exhibited higher ribavirin plasma exposures compared to patients with normal renal function (creatinine clearance >80 mL/min) receiving the standard dose of Copegus (see section 2.2.1 and section 3.2.2).

In a study of patients with ESRD receiving chronic hemodialysis, most of whom received hematopoietic growth factors, Copegus was safely administered at a dose of 200 mg daily. In this study, ESRD patients receiving chronic hemodialysis who were administered a 200 mg daily dose exhibited ribavirin plasma exposures that were approximately 20% lower compared to patients with normal renal function receiving the standard 1000/1200 mg Copegus daily dose (see section 2.2.1 and section 3.2.2).

2.5.6 Hepatic Impairment

No pharmacokinetic interaction appears between ribavirin and hepatic function. Therefore, no dose adjustment of Copegus is required in patients with hepatic impairment. The use of peginterferon alfa-2a of interferon-2a is contraindicated in patients with decompensated liver disease.

2.6 Undesirable Effects

2.6.1 Clinical Trials

The types and frequency of adverse events with combination therapy are consistent with the known safety profile of interferon alfa-2a or peginterferon alfa-2a and the undesirable effects associated with ribavirin.

Chronic Hepatitis C

In comparison to 48 weeks of treatment with Copegus 1000/1200 mg and peginterferon alfa-2a 180 mcg, reducing treatment duration to 24 weeks and Copegus dose to 800 mg resulted in reductions in serious adverse events (11% vs 3%), premature withdrawals for safety reasons (13% vs 5%), and the need for Copegus dose modification (39% vs 19%) .

Chronic Hepatitis C prior non-responder patients

In a clinical trial which included 72 and 48 weeks treatments of prior pegylated interferon alfa-2b/ribavarin non-responder patients, the frequency of withdrawal from peginterferon alfa-2a treatment was 12% and Copegus treatment was 13% due to adverse events or laboratory abnormalities, for patients in the 72-week arms. In comparison, in 48 week treatment arms, 6% withdrew from peginterferon alfa-2a and 7% withdrew from Copegus treatment. Similarly for patients with cirrhosis, withdrawal rates from peginterferon alfa-2a and Copegus treatment were higher in the 72-week treatment arms (13% and 15%), compared to the 48-week arms (6% and 6%). Patients who withdrew from previous therapy due to hematological toxicity were excluded from enrolling in this trial.

In another clinical trial, patients with advanced fibrosis or cirrhosis (Ishak score of 3 to 6) who had not responded to previous treatment were enrolled with baseline platelet counts as low as 50,000/mm^3 and treated for 48 weeks. Due to a high prevalence of the advanced cirrhosis/fibrosis state and the low baseline platelet counts among patients in this study, the frequency of hematologic lab abnormalities in the first 20 weeks of the trial were as follows: hemoglobin < 10 g/dL, 26.3%; ANC < 750/mm^3, 30%; and platelet < 50,000/mm^3, 13% (see section 2.4 Warnings and Precautions).

HIV-HCV Co-infection

In HIV-HCV co-infected patients, the clinical adverse events reported on peginterferon alfa-2a, alone or in combination with Copegus, were similar to that observed in HCV mono-infected patients. Limited safety data (N = 51) is available in co-infected patients with CD4+ cell counts < 200/µl. In study NR 15961, the incidence of withdrawal from treatment for clinical adverse events, laboratory abnormalities or AIDS-defining events was 16% for peginterferon alfa-2a monotherapy, and 15% for peginterferon alfa-2a in combination with Copegus 800 mg, given for 48 weeks. Respectively, 4% or 3% of patients required discontinuation of peginterferon alfa-2a or peginterferon alfa-2a /Copegus for laboratory abnormalities. In combination therapy, peginterferon alfa-2a dose modification occurred in 39%, and Copegus dose modification occurred in 37%, of the co-infected patients. Serious adverse events were reported in 21% and 17% of those receiving peginterferon alfa-2a monotherapy or in combination with Copegus, respectively.

Peginterferon alfa-2a containing treatment was associated with an on-treatment reduction in absolute CD4+ cell count without a reduction in CD4+ cell percentage. CD4+ cell count indices returned to baseline values during the follow-up period of the study. Peginterferon alfa-2a containing treatment had no apparent negative impact on the control of HIV viremia during therapy or follow-up.

Table 6 shows those undesirable effects occurring in ≥10% of HCV patients, as well as in HIV-HCV co-infected patients, who have received different treatment regimens of Copegus in combination with peginterferon alfa-2a. Adverse events reported in patients receiving ribavirin in combination with alfa interferon are essentially the same as those reported for Copegus in combination with peginterferon alfa-2a.

Table 6. Adverse Reactions (≥10% Incidence)

	HCV		**HIV-HCV**	**HCV non-responder to prior peginterferon alfa-2b therapy**
	Copegus 800 mg + Peginterferon alfa-2a 180 mcg (NV15492) 24 weeks N=207	Copegus 1000 or 1200 mg + Peginterferon alfa-2a 180 mcg (NV15801+ NV15942) 48 weeks N=887	Copegus 800 mg + Peginterferon alfa-2a 180 mcg (NR15961) 48 weeks N=288	Copegus 1000 or 1200 mg + Peginterferon alfa-2a 180 mcg (MV17150) 72 weeks N=156
Body System	%	%	%	%
Metabolism & nutrition disorders				
Anorexia	20%	27%	23%	15%
Weight decrease	2%	7%	16%	9%
Psychiatric disorders				
Insomnia	30%	32%	19%	29%
Irritability	28%	24%	15%	17%
Depression	17%	21%	22%	16%
Concentration impairment	8%	10%	2%	5%
Nervous system disorders				
Headache	48%	47%	35%	32%
Dizziness	13%	15%	7%	10%
Respiratory, thoracic and mediastinal disorders				
Dyspnea	11%	13%	7%	11%
Cough	8%	13%	3%	17%

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Gastrointestinal disorders				
Nausea	29%	28%	24%	24%
Diarrhea	15%	14%	16%	13%
Abdominal pain	9%	10%	7%	9%
Skin and subcutaneous tissue disorders				
Alopecia	25%	24%	10%	18%
Pruritus	25%	21%	5%	22%
Dermatitis	15%	16%	1%	1%
Dry skin	13%	12%	4%	17%
Musculoskeletal, connective tissue and bone disorders				
Myalgia	42%	38%	32%	22%
Arthralgia	20%	22%	16%	15%
General disorders and administration site conditions				
Fatigue	45%	49%	40%	36%
Pyrexia	37%	39%	41%	20%
Rigors	30%	25%	16%	12%
Injection site reaction	28%	21%	10%	12%
Asthenia	18%	15%	26%	30%
Pain	9%	10%	6%	6%

Undesirable effects reported in ≥1% but <10% on Pegasys/Copegus combination or Pegasys monotherapy in HCV and HIV-HCV patients were:

Infections and infestations: herpes simplex, URI infection, bronchitis, oral candidiasis

Blood and the lymphatic system disorders: lymphadenopathy, anemia, thrombocytopenia

Endocrine disorders: hypothyroidism, hyperthyroidism

Neuropsychiatric disorders: memory impairment, taste disturbance, paraesthesia, hypoesthesia, tremor, weakness, emotional disorders, mood alteration, nervousness, aggression, libido decreased, migraine, somnolence, hyperesthesia, nightmares, syncope, anxiety

Eye disorders: vision blurred, xerophthalmia, eye inflammation, eye pain

Ear and labyrinth disorders: vertigo, earache

Cardiac disorders: palpitations, edema peripheral, tachycardia

Vascular disorders: flushing

Respiratory, thoracic and mediastinal disorders: sore throat, rhinitis, nasopharyngitis, sinus congestion, dyspnoea exertional, epistaxis

Gastrointestinal disorders: vomiting, dyspepsia, flatulence, dry mouth, mouth ulceration, gingival bleeding, stomatitis, dysphagia, glossitis

Skin and subcutaneous tissue disorders: skin disorder, rash, eczema, psoriasis, urticaria, photosensitivity reaction, sweating increased, night sweats

Musculoskeletal, connective tissue and bone disorders: bone pain, back pain, neck pain, muscle cramps, muscle weakness, musculoskeletal pain, arthritis

Reproductive system and breast disorders: impotence

General disorders and administration site conditions: influenza-like illness, malaise, lethargy, hot flushes, chest pain, thirst

Other adverse reactions reported in ≥ 1% to ≤ 2% of HIV-HCV patients receiving Pegasys/Copegus combination included: hyperlactacidemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

As with other alpha interferon therapies, uncommon to rare cases of the following serious adverse events have been reported in patients receiving Pegasys/Copegus combination or Pegasys monotherapy during clinical trials: lower respiratory tract infection, skin infection, otitis externa, endocarditis, suicide, substance overdose, hepatic dysfunction, fatty liver, cholangitis, malignant hepatic neoplasm, peptic ulcer, gastrointestinal bleeding, pancreatitis, arrhythmia, atrial fibrillation, pericarditis, autoimmune phenomena (e.g., ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE), myositis, peripheral neuropathy, sarcoidosis, interstitial pneumonitis with fatal outcome, pulmonary embolism, corneal ulcer, coma and cerebral hemorrhage, TTP, psychotic disorder and hallucination.

Very rarely, alfa interferon including Pegasys, used alone or in combination with ribavirin may be associated with pancytopenia including aplastic anemia.

Laboratory values: In clinical trials of Copegus in combination with peginterferon alfa-2a or interferon alfa-2a, the majority of cases of abnormal laboratory values were managed with dose modifications (see section 2.2.1, Special Dosage Instructions).

Hemolysis is the defining toxicity of ribavirin therapy. A decrease in hemoglobin levels to <10 g/dL was observed in up to 15% of patients treated for 48 weeks with Copegus 1000/1200 mg in combination with peginterferon alfa-2a and up to 19% of patients in combination with interferon alfa-2a. When Copegus 800 mg was combined with peginterferon alfa-2a for 24 weeks, 3% of patients had a decrease in hemoglobin levels to <10 g/dL. It is not expected that patients will need to discontinue therapy because of decrease in hemoglobin levels alone. In most cases the decrease in hemoglobin occurred early in the treatment period and stabilized concurrently with a compensatory increase in reticulocytes.

Laboratory values for HIV-HCV co-infected patients

Although hematological toxicities of neutropenia, thrombocytopenia, and anemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment. Decrease in ANC levels below 500 cells/mm^3 was observed in 13% and 11% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm^3 was observed in 10% and 8% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Anemia (haemoglobin < 10g/dL) was reported in 7% and 14% of patients treated with peginterferon alfa-2a monotherapy or in combination therapy, respectively.

Please refer to the label of peginterferon alfa-2a or interferon alfa-2a for additional information.

2.6.2 Post Marketing

During the post-marketing period, erythema multiforme, Steven Johnson syndrome, toxic epidermal necrolysis, pure red cell aplasia (PRCA) and homicidal ideation have been reported very rarely with combination therapy of Pegasys and ribavirin.

Dehydration has been reported rarely with combination therapy of Copegus and alpha interferons.

As with other alpha interferons, serous retinal detachment has been reported with Pegasys and Copegus combination therapy.

As with other alpha interferons, liver and renal graft rejections have been reported on Pegasys, alone or in combination with Copegus.

2.7 Overdose

No cases of overdose of Copegus have been reported in clinical trials. Hypocalcemia and hypomagnesemia have been observed in persons administrated dosages greater than four times the maximal recommended dosages. In many of these cases ribavirin was administered intravenously. Ribavirin is not effectively removed by hemodialysis.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Ribavirin is a synthetic nucleoside analog that shows *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with alfa interferon or peginterferon alfa-2a exerts its effects against HCV is unknown.

Oral formulations of ribavirin monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that ribavirin monotherapy had no effect on eliminating hepatitis virus (HCV RNA) or improving hepatic histology after 6 to 12 months of therapy and 6 months of follow-up.

3.1.2 Clinical/Efficacy Studies

Copegus in combination with peginterferon alfa-2a

Chronic Hepatitis C

Study results in naïve patients

Efficacy and safety of the combination of Copegus and peginterferon alfa-2a were established in two pivotal studies (NV15801 + NV15942), including a total of 2405 patients. The study population comprised interferon-naïve patients with CHC confirmed by detectable levels of serum HCV RNA, elevated levels of ALT, and a liver biopsy consistent with chronic hepatitis C infection.

Study NV15801 (1121 patients treated) compared the efficacy of 48 weeks of treatment with peginterferon alfa-2a (180 mcg once weekly) and Copegus (1000/1200 mg daily) with either peginterferon alfa-2a monotherapy or combination therapy with interferon-alfa-2b and ribavirin. The combination of peginterferon alfa-2a and Copegus was significantly more efficacious than the combination of interferon alfa-2b and ribavirin or peginterferon alfa-2a monotherapy (see Table 7).

Study NV15942 (1284 patients treated) compared the efficacy of two durations of treatment (24 weeks with 48 weeks) and two dosages of Copegus (800 mg with 1000/1200 mg).

In patients infected with genotype 1, the sustained virological response was higher after 48 weeks of treatment than after 24 weeks (p=0.001) and with the higher dose of Copegus (p=0.005). However, for patients infected with genotype 2/3 there was no statistically significant difference between 48 and 24 weeks of treatment and between the low and high dose of Copegus (see Table 8). These patterns of response were not influenced by viral load or presence/absence of cirrhosis, therefore treatment recommendations are independent of these baseline characteristics. Virological response was defined as undetectable HCV RNA as measured by the COBAS AMPLICOR™ HCV Test, version 2.0 (limit of detection 100 copies/ml equivalent to 50 International Units/ml) and sustained response as one negative sample approximately 6 months after the end of therapy.

Table 7. Virological Response in the Overall Population (including non-cirrhotic and cirrhotic patients)

	Study NV15942	Study NV15801	
	Copegus 1000/1200 mg + **Peginterferon alfa-2a** 180 mcg (N=436) 48 weeks	**Copegus** 1000/1200 mg + **Peginterferon alfa-2a** 180 mcg (N=453) 48 weeks	**Ribavirin** 1000/1200 mg + **Interferon alfa-2b** 3 MIU (N=444) 48 weeks
Response at end of Treatment	68%	69%	52%
Overall Sustained Response	63%	54%*	45%*

*95% CI for difference: 3% to 16% p-value (stratified Cochran-Mantel-Haenszel test) = 0.003

Table 8 Sustained Virological Response based on Genotype and Viral Load after Copegus Combination Therapy with Pegasys

	Study NV15942				Study NV15801	
	Copegus 800 mg + **PEG-IFN alfa-2a** 180 mcg 24 weeks	**Copegus** 1000/1200 mg + **PEG-IFN alfa-2a** 180 mcg 24 weeks	**Copegus** 800 mg + **PEG-IFN alfa-2a** 180 mcg 48 weeks	**Copegus** 1000/1200 mg + **PEG-IFN alfa-2a** 180 mcg 48 weeks	**Copegus** 1000/1200 mg + **PEG-IFN alfa-2a** 180 mcg 48 weeks	**Ribavirin** 1000/1200 mg + **Interferon alfa-2b** 3 MIU 48 weeks
Genotype 1 Low viral load High viral load	29% (29/101) 41% (21/51) 16% (8/50)	42% (49/118) † 52% (37/71) 26% (12/47)	41% (102/250) 55% (33/60) 36% (69/190)	**52%** (142/271) *† **65%** (55/85) **47%** (87/186)	45% (134/298) 53% (61/115) 40% (73/182)	36% (103/285) 44% (41/94) 33% (62/189)
Genotype 2/3 Low viral load High viral load	**84%** (81/96) **85%** (29/34) **84%** (52/62)	81% (117/144) 83% (39/47) 80% (78/97)	79% (78/99) 88% (29/33) 74% (49/66)	80% (123/153) 77% (37/48) 82% (86/105)	71% (100/140) 76% (28/37) 70% (72/103)	61% (88/145) 65% (34/52) 58% (54/93)
Genotype 4	0% (0/5)	67% (8/12)	63% (5/8)	82% (9/11)	77% (10/13)	45% (5/11)

*Copegus 1000/1200 mg + peginterferon alfa-2a 180 mcg, 48 w vs. Copegus 800 mg + peginterferon alfa-2a 180 mcg, 48 w: Odds Ratio (95% CI) = 1.52 (1.07 to 2.17) p-value (stratified Cochran-Mantel-Haenszel test) = 0.020
†Copegus 1000/1200 mg + peginterferon alfa-2a 180 mcg, 48 w vs. Copegus 1000/1200 mg + peginterferon alfa-2a 180 mcg, 24 w: Odds Ratio (95% CI) = 2.12 (1.30 to 3.46) p-value (stratified Cochran-Mantel-Haenszel test) = 0.002

The possibility to consider shortening treatment duration to 24 weeks in genotype 1 and 4 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response at week 4 in study NV15942 (see Table 9).

Table 9 Sustained Virological Response Based on Rapid Viral Response at week 4 for Genotype 1 and 4 after Pegasys Combination Therapy with Ribavirin in HCV Patients.

Study NV15942		
	Pegasys 180 mcg & Ribavirin 1000/1200 mg 24 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 48 weeks
Genotype 1 RVR **Low viral load** **High viral load**	90% (28/31) 93% (25/27) 75% (3/4)	92% (47/51) 96% (26/27) 88% (21/24)
Genotype 1 non RVR **Low viral load** **High viral load**	24% (21/87) 27% (12/44) 21% (9/43)	43% (95/220) 50% (31/62) 41% (64/158)
Genotype 4 RVR	(5/6)	(5/5)
Genotype 4 non RVR	(3/6)	(4/6)

Low viral load= ≤ 800,000 IU/mL; High viral load= > 800,000 IU/mL
RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 10).

In study NV17317 in patients infected with viral genotype 2 or 3, all patients received peginterferon alfa-2a 180 mcg sc qw and a Copegus dose of 800 mg and were randomized to treatment for either 16 or 24 weeks. Overall treatment for 16 weeks was not equivalent to treatment for 24 weeks (see Table 10). Treatment for 16 weeks resulted in lower sustained viral response (65%) than treatment for 24 weeks (76%). However, a retrospective analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline showed that the sustained viral response achieved with 16 weeks of treatment was comparable to that achieved with 24 weeks of treatment (89% and 94%, respectively) (see Table 10).

Table 10 Sustained Virological Response Based on Rapid Viral Response at week 4 for Genotype 2 and 3 after Pegasys Combination Therapy with Ribavarin in HCV Patients

Study NV17317		
	Pegasys 180 mcg & **Ribavirin** 800 mg 16 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks
Genotype 2 or 3	65% (443/679)	76% (478/630)
Genotype 2 or 3 RVR Low viral load High viral load	82% (378/461) 89% (147/166) 78% (231/295)	90% (370/410) 94% (141/150) 88% (229/260)
Genotype 2 or 3 non RVR Low viral load High viral load	30% (65/218) 44% (22/50) 26% (43/168)	49% (108/220) 50% (25/50) 49% (83/170)

Low viral load = ≤ 800,000 IU/mL at baseline; High viral load = > 800,000 IU/mL at baseline, RVR = rapid viral response (HCV RNA negative) by week 4.

Chronic Hepatitis C prior treatment non-responder patients

In study MV17150, patients who were previous non-responders to pegylated interferon alfa-2b plus ribavarin therapy were randomized to four different treatments: peginterferon alfa-2a 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 60 weeks; peginterferon alfa-2a 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 36 weeks; peginterferon alfa-2a 180 mcg/week for 72 weeks; or peginterferon alfa-2a 180 mcg/week for 48 weeks. All patients received ribavarin (1,000 or 1,200 mg/day) in combination with peginterferon alfa-2a. All treatments had 24 week treatment free follow up. The sustained virological responses from a pooled analysis comparing duration of therapy or peginterferon alfa-2a induction dosing are summarized Table 11.

Table 11 Sustained Virological Response in Previous PEG-IFN alfa-2b/Ribavarin Non-Responders: Pooled Treatment Comparisons

	MV17150			
	72 week Groups N = 473	48 week Groups N = 469	360 mcg Groups N = 473	180 mcg Groups N = 469
SVR	16%*	8%*	13%	10%

95% confidence interval (CI) of 1.40 to 3.52) and a p value of 0.00061

The sustained virological response rate after 72 weeks treatment was superior to that after 48 weeks.

Differences in sustained virological response based on treatment duration and demographics found in study MV17150 are displayed in Table 12.

Table 12 Sustained Virological Response after treatment with Copegus and Peginterferon alfa 2a Combination Therapy in Non-responders to Previous Treatment with Peginterferon alfa 2b/ribavarin.

	Peginterferon alfa 2b/ribavirin NRs Re-treated for 48 weeks % (N)	**Peginterferon alfa 2b/ribavirin NRs Re-treated for 72 weeks % (N)**
Overall NR	8% (38/469)	16% (74/473)
Genotype 1/4	7% (33/450)	15% (68/457)
Genotype 2/3	25% (4/16)	33% (5/15)
Genotype		
1	7% (31/426)	14% (60/430)
2	0 (0/4)	33% (1/3)
3	33% (4/12)	33% (4/12)
4	8% (2/24)	30% (8/27)
Baseline Viral Load		
HVL (greater than 800,000 IU/mL)	7% (25/363)	12% (46/372)
LVL (less than or equalto 800,000 IU/mL)	13% (11/84)	31% (27/86)

In the HALT-C study patients with chronic hepatitis C and advanced fibrosis or cirrhosis who had not responded to previous treatment with interferon alfa or pegylated interferon alfa monotherapy or combination ribavarin therapy were treated with peginterferon alfa-2a 180 mcg/week and Copegus 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on peginterferon alfa-2a plus Copegus combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. Sustained virological response varied depending upon the previous treatment regimen. Treatment outcome was poorest among patients who were non-responders to pegylated interferon in combination with ribavarin, identifying the most difficult to treat subpopulation of non-responder patients, and comparable with the sustained virological response rate observed in the 48 week treatment arms of MV17150. Despite higher sustained virological response in non-responders to interferon or pegylated interferon monotherapy, efficacy in these less difficult to treat non-responders remains substantially lower than what is achievable in treatment-naïve patients (see Table 13).

Table 13 SVR rates by Treatment Duration and Non-responder Population

Treatment Duration	**Interferon**	**Pegylated Interferon**	**Interferon plus Ribavirin**	**Pegylated interferon plus Ribavirin**	
48 weeks	27% (70/255)*	34% (13/38)*	13% (90/692)*	11% (7/61)*	8% (38/469)**

72 weeks	-	-	-	-	16% (74/473)**

* data from HALT-C
** data from MV17150

Chronic Hepatitis C prior treatment relapser patients

In a study in predominantly genotype 1 chronic hepatitis C patients who had relapsed after 48 weeks of combination treatment with pegylated interferon alfa-2 plus ribavarin, patients were treated for 72 weeks with the combination of either peginterferon alfa-2a 180 mcg/week plus weight-based Copegus daily or consensus interferon (9 mcg) daily plus weight-based Copegus daily. The sustained virological response was 42% for patients treated with peginterferon alfa-2a and ribavarin combination therapy for 72 weeks.

In an open-label, study in genotype 2 and 3 chronic hepatitis C patients who relapsed after treatment for 24 weeks with peginterferon alfa-2a and Copegus combination therapy, patients were treated with peginterferon alfa-2a 180 mcg/week and Copegus 1000 or 1200 mg (by weight) daily combination therapy for 48 weeks and then followed treatment-free for 24 weeks. The sustained virological response was 64%.

HIV-HCV Co-infection

In study NR15961, 860 HIV-HCV co-infected patients were randomized and treated with peginterferon alfa-2a 180 mcg/week and placebo, peginterferon alfa-2a 180 mcg/week and ribavarin 800 mg/day or interferon alfa-2a 3 MIU three times weekly and ribavarin 800 mg/day for 48 weeks followed by a 24 week treatment-free follow-up. The sustained virologic responses for the three treatment groups are summarized for all patients and by genotype in Table 14.

Table 14 Sustained Virologic Response in HIV-HCV Co-infected Patients

	PEGASYS 180mcg + Placebo 48 weeks	**PEGASYS** 180mcg + **COPEGUS** 800mg 48 weeks	**Interferon alfa-2a** 3MIU + **COPEGUS** 800mg 48 weeks
All patients	20% (58/286)*	40% (116/289)*	12% (33/285)*
Genotype 1	14% (24/175)	29% (51/176)	7% (12/171)
Genotype 2/3	36% (32/90)	62% (59/95)	20% (18/89)

* Pegasys 180 mcg, Copegus 800 mg vs. Interferon alfa-2a 3MIU Copegus 800 mg: Odds Ratio (95%CI) = 5.40 (3.42 to 8.54), p-value (stratified Cochran-Mantel-Haenszel test) = <0.0001

* Pegasys 180 mcg, Copegus 800 mg vs. Pegasys 180 mcg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), p-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

Ribavarin in combination with interferon alfa-2a

The therapeutic efficacy of interferon alfa-2a alone and in combination with oral ribavirin was compared in clinical trials in naïve (previously untreated) and relapsed patients who had virologically, biochemically and histologically documented chronic hepatitis C. Six months after end of treatment sustained biochemical and virological response as well as histological improvement were assessed.

A statistically significant 10-fold increase (from 4% to 43%; p <0.01) in sustained virological and biochemical response was observed in relapsed patients (M23136; N=99). The favorable profile of the combination therapy was also reflected in the response rates relative to HCV genotype or baseline viral load. In the combination and interferon monotherapy arms, respectively, the sustained response rates in patients with HCV genotype-1 were 28% versus 0% and with genotype non-1 were 58% versus 8%. In addition, the histological improvement favored the combination therapy. Supportive favorable results (monotherapy vs combination; 6% vs 48%, p<0.04) from a small published study in naïve patients (N=40) were reported using interferon alfa-2a (3 MIU 3 times per week) with ribavirin.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Ribavirin is absorbed rapidly following oral administration of a single dose of Copegus (median T_{max} = 1-2 hours). The mean terminal phase half-life of ribavirin following single doses of Copegus range from 140 to 160 hours. Ribavirin data from the literature demonstrates absorption is extensive with approximately 10% of a radiolabeled dose excreted in the feces. However, absolute bioavailability is approximately 45%-65%, which appears to be due to first pass metabolism. There is a linear relationship between dose and AUC_{tf} following single doses of 200-1200 mg ribavirin. Mean apparent oral clearance of ribavirin following single 600 mg doses of Copegus ranges from 22 to 29 litres/hour. Volume of distribution is approximately 4500 1itres following administration of Copegus. Ribavirin does not bind to plasma proteins.

Food effect

The bioavailability of a single oral 600 mg dose Copegus was increased by coadministration of a high fat meal. The ribavirin exposure parameters of $AUC_{(0-192h)}$ and C_{max} increased by 42% and 66%, respectively, when Copegus was taken with a high fat breakfast compared to being taken in the fasted state. The clinical relevance of results from this single dose study is unknown. Ribavirin exposure after multiple dosing when taken with food was comparable in patients receiving peginterferon alfa-2a and Copegus and interferon alfa-2b and ribavirin. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food.

3.2.2 Distribution

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following a single oral dose of Copegus (intra-subject variability of ≤25% for both AUC and C_{max}), which may be due to extensive first pass metabolism and transfer within and beyond the blood compartment.

Ribavirin transport in non-plasma compartments has been most extensively studied in red cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the high volume of distribution of ribavirin. The ratio of whole blood: plasma ribavirin concentrations is approximately 60:1; the excess of ribavirin in whole blood exists as ribavirin nucleotides sequestered in erythrocytes.

3.2.3 Metabolism

Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway, 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxyacid metabolite. Ribavirin and both its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally.

Upon multiple dosing, ribavirin accumulates extensively in plasma with a six-fold ratio of multiple-dose to single-dose AUC_{12hr} based on literature data. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations of approximately 2200 ng/ml.

3.2.4 Elimination

Upon discontinuation of dosing the half-life was approximately 300 hours, which probably reflects slow elimination from non-plasma compartments.

3.2.5 Pharmacokinetics in Special Population

Patients with renal impairment: The apparent clearance of ribavirin is reduced in patients with creatinine clearance ≤50 mL/min, including patients with ESRD on chronic hemodialysis, exhibiting approximately 30% of the value found in patients with normal renal function (creatinine clearance >80 mL/min). Poor tolerability was observed in Patients not on chronic hemodialysis with moderate or severe renal impairment (creatinine clearance ≤50 mL/min) receiving daily doses of 600 mg and 400 mg of Copegus, respectively, requiring frequent dose reductions. Despite reduced Copegus dosing in these patients, ribavirin plasma exposure (AUC) in moderate and severe impairment was found to be respectively, 36% and 25% higher compared to patients with normal renal function receiving the standard Copegus dose. Increased rates of adverse drug reactions, mainly anaemia, were observed in patients with moderate and severe renal impairment receiving the doses evaluated in this study. Patients with ESRD on chronic hemodialysis tolerated 200 mg daily doses of Copegus and exhibited mean ribavirin exposure (AUC) approximately 80% of the value found in patients with normal renal function (see section 2.2.1). Plasma ribavirin is removed by hemodialysis with an extraction ratio of approximately 50%.

Based on pharmacokinetic modelling and simulation, dose adjustments are recommended in patients with significant renal impairment (see section 2.2.1). These adjusted doses are expected to provide ribavirin plasma exposures similar to those achieved in patients with normal renal function receiving the standard Copegus dose. Except for the 200 mg daily dose in ESRD, these recommended doses have not been investigated in clinical trials.

Patients with hepatic dysfunction: Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction are similar to those of normal controls.

Elderly patients (≥ 65 years of age): Specific pharmacokinetic evaluations for elderly subjects have not been performed. However, in a published population pharmacokinetic study, age was not a key factor in the kinetics of ribavirin; renal function is the determining factor.

Patients under the age of 18 years: Specific pharmacokinetic studies have not been fully evaluated in patients under the age of 18 years. Copegus in combination with peginterferon alfa-2a or interferon alfa-2a is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Race: A pharmacokinetic study in 42 subjects demonstrated there is no clinically significant difference in ribavirin pharmacokinetics among Black (n=14), Hispanic (n=13) and Caucasian (n=15) subjects.

3.3 Preclinical Safety

3.3.1 Carcinogenicity

In a p53 (+/-) mouse carcinogenicity study and a rat 2-year carcinogenicity study at doses up to the maximum tolerated doses of 100 mg/kg/day and 60 mg/kg/day, respectively, ribavirin was not oncogenic. On a body surface area basis, these doses are approximately 0.5 and 0.6 times the maximum recommended human 24-hour dose of ribavirin.

3.3.2 Impairment of Fertility

In repeat dose studies in mice to investigate ribavirin-induced testicular and sperm effects, abnormalities in sperm occurred at doses in animals well below therapeutic doses. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity occurred within one or two spermatogenic cycles.

3.3.3 Other

Erythrocytes are a primary target of toxicity for ribavirin in animal studies. Anemia occurs shortly after initiation of dosing, but is rapidly reversible upon cessation of treatment.

Genotoxicity studies have demonstrated that ribavirin does exert some genotoxic activity. Ribavirin was active in an in-vitro Transformation Assay. Genotoxic activity was observed *in vivo* mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. The potential of carcinogenic risk to humans cannot be excluded.

Administration of ribavirin and peginterferon alfa 2a in combination did not produce any unexpected toxicity in monkeys. The major treatment-related change was reversible mild to moderate anemia, the severity of which was greater than that produced by either active substance alone.

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Tablet Excipients:

Tablet core:
Pregelatinized starch
Sodium starch glycolate
Microcrystalline cellulose
Maize starch
Magnesium stearate,

Film-coating:
Hypromellose
Talc
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)
Ethylcellulose aqueous dispersión
Triacetin

4.2 Stability

This medicine should not be used after the expiry date (EXP) shown on the pack.

Do not store above 30ºC
See also outer pack for storage remark.

4.3 Storage

Copegus is supplied in a high density polyethylene (HDPE) bottle with a child-resistant polypropylene screw cap

4.4 Special Instructions for Use, Handling and Disposal

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems" if available in your location.

5. PACKS

Film-coated tablets ……..42, 168

Medicine: keep out of reach of children

MYCopegus1018/CDS16.0

Roche

Made for
F. Hoffmann-La Roche Ltd,
Basel, Switzerland
by Patheon Inc, Mississauga,Canada.

Revision Date: Oct 2018