

Copegus Film-coated tablets

Core Safety Profile (CSP)

Based on:

**Copegus EU SmPC, valid on 31 August 2012 HLR #
Corresponding to approved CSP from PSUR #10, 16 February 2012**

4.2 Posology and method of administration

Treatment should be initiated, and monitored, by a physician experienced in the management of chronic hepatitis C.

Method of Administration

Copegus film-coated tablets are administered orally in two divided doses with food (morning and evening). Due to the teratogenic potential of ribavirin, the tablets should not be broken or crushed.

Posology

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 SPC of peginterferon alfa-2a or interferon alfa-2a for further information on dosage and duration of treatment when Copegus is to be used in combination with either of these products.

Posology in combination with peginterferon alfa-2a:

Dose to be administered

The recommended dose of Copegus in combination with peginterferon alfa-2a solution for injection depends on viral genotype and the patient's body weight (see Table 1).

Duration of treatment

The duration of combination therapy with peginterferon alfa-2a 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) ($\leq 800,000$ 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 (see 5.1). 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.

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 only 16 weeks may be considered in selected patients infected with genotype 2 or 3 with LVL ($\leq 800,000$ IU/mL) at baseline who become HCV negative by week 4 of treatment and remain HCV negative by week 16. Overall 16 weeks of treatment may be associated with a lower chance of response and is associated with a higher risk of relapse than a 24 week treatment duration (see section 5.1). 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 24 weeks treatment duration. Shortening the treatment duration in patients infected with genotype 2 or 3 with HVL ($> 800,000$ IU/mL) 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 Table 1).

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 200/400 mg tablets
Genotype 1 LVL with RVR*	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	24 weeks or 48 weeks	5 x 200 mg (2 morning, 3 evening) 6 x 200 mg (3 morning, 3 evening)
Genotype 1 HVL with RVR*	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	48 weeks	5 x 200 mg (2 morning, 3 evening) 6 x 200 mg (3 morning, 3 evening)
Genotype 4 with RVR*	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	24 weeks or 48 weeks	5 x 200 mg (2 morning, 3 evening) 6 x 200 mg (3 morning, 3 evening)
Genotype 1 or 4 without RVR*	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	48 weeks	5 x 200 mg (2 morning, 3 evening) 6 x 200 mg (3 morning, 3 evening)
Genotype 2 or 3 LVL with RVR**	800 mg(a)	16 weeks(a) or 24 weeks	4 x 200 mg (2 morning, 2 evening) or 2 x 400 mg (1 morning, 1 evening)
Genotype 2 or 3 HVL with RVR**	800 mg	24 weeks	4 x 200 mg (2 morning, 2 evening) or 2 x 400 mg (1 morning, 1 evening)
Genotype 2 or 3 without RVR**	800 mg	24 weeks	4 x 200 mg (2 morning, 2 evening) or 2 x 400 mg (1 morning, 1 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= $\leq 800,000$ IU/mL; HVL= $> 800,000$ IU/mL

^(a) It is presently not clear whether a higher dose of Copegus (e.g.1000/1200 mg/day

based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The ultimate clinical impact of a shortened initial treatment of 16 weeks instead of 24 weeks is unknown, taking into account the need for retreating non-responding and relapsing patients.

Chronic hepatitis C – treatment-experienced patients

The recommended dose of Copegus, in combination with 180 micrograms once weekly of peginterferon alfa-2a, is 1000 milligrams daily or 1200 milligrams daily for patients <75 kg and ≥75 kg, respectively, regardless of genotype.

Patients who have detectable virus at week 12 should stop therapy. The recommended total duration of therapy is 48 weeks. If patients infected with virus genotype 1, not responding to prior treatment with peginterferon and ribavirin are considered for treatment, the recommended total duration of therapy is 72 weeks (see section 5.1).

HIV-HCV Co-infection

The recommended dosage for Copegus in combination with 180 micrograms once weekly, for 48 weeks, of peginterferon alfa-2a is as follows:

- patients infected with HCV genotype 1 < 75 kg: 1000 mg daily
- patients infected with HCV genotype 1 ≥ 75 kg: 1200 mg daily
- patients infected with HCV genotype other than 1 should receive 800 milligrams daily. A duration of therapy less than 48 weeks has not been adequately studied.

Predictability of response and non-response – treatment-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 peginterferon Combination Therapy		
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 has been observed in HIV-HCV co-infected patients treated with peginterferon alfa-2a monotherapy or in combination with ribavirin (100% (130/130) or 98% (83/85), respectively). Positive predictive values of 45% (50/110) and 70% (59/84) were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Predictability of response and non-response – treatment-experienced patients

In non-responder patients re-treated for 48 or 72 weeks, viral suppression at week 12 (undetectable HCV RNA defined as <50 IU/ml) has been shown to be predictive for sustained virological response. The probabilities of not achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was not achieved at week 12 were 96% (363 of 380) and 96% (324 of 339), respectively. The probabilities of

achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was achieved at week 12 were 35% (20 of 57) and 57% (57 of 100), respectively.

Posology in combination with 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			
Patient weight (kg)	Daily Copegus dose	Duration of treatment	Number of 200 mg tablets
<75	1,000 mg	24 or 48 weeks	5 (2 morning, 3 evening)
≥75	1,200 mg	24 or 48 weeks	6 (3 morning, 3 evening)

Dosage modification for adverse reactions

Please refer to the SPC 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. Guidelines were developed in clinical trials for dose modification (see **Dosage Modification Guidelines for Management of Treatment-Emergent Anaemia**, Table 4).

If intolerance persists after dose adjustment, discontinuation of Copegus or both Copegus and peginterferon alfa-2a or interferon alfa-2a may be needed.

Table 4 Dosage Modification Guidelines for Management of Treatment-Emergent Anaemia		
Laboratory Values	Reduce only Copegus dose to 600 mg/day* if:	Discontinue Copegus if: **
Haemoglobin in Patients with No Cardiac Disease	<10 g/dl	<8.5 g/dl
Haemoglobin: Patients with History of Stable Cardiac Disease	>2 g/dl decrease in haemoglobin during any 4 week period during treatment (permanent dose reduction)	<12 g/dl despite 4 weeks at reduced dose

*Patients whose dose of Copegus is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets or one 400 mg tablet 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.

Special populations

Use in renal impairment: The recommended dose regimens (adjusted by the body weight cutoff of 75 kg) of ribavirin give rise to substantial increases in plasma concentrations of ribavirin in patients with renal impairment. There are insufficient data on the safety, efficacy and pharmacokinetics of ribavirin in patients with serum creatinine > 2 mg/dl or creatinine clearance < 50 ml/min, whether or not on haemodialysis, to support specific recommendations for dose adjustments (see section 5.2). Therefore, ribavirin should be used in such patients only when this is considered to be essential. Therapy should be initiated (or continued if renal impairment develops while on therapy) with extreme caution and intensive monitoring of haemoglobin concentrations, with corrective action as may be necessary, should be employed throughout the treatment period. (see section 4.4).

Use in hepatic impairment: Hepatic function does not affect the pharmacokinetics of ribavirin (see section 5.2). Therefore, no dose adjustment of Copegus is required in patients with hepatic impairment. The use of peginterferon alfa-2a and interferon alfa-2a is contraindicated in patients with decompensated cirrhosis and other forms of severe hepatic impairment.

Use in elderly patients over the age of 65: There does not appear to be a significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to administration of Copegus.

Use in patients under the age of 18 years: Treatment with Copegus is not recommended for use in children and adolescents (<18 years) due to insufficient data on safety and efficacy in combination with peginterferon alfa-2a and interferon alfa-2a. Only limited safety and efficacy data are available in children and adolescents (6-18 years) in combination with peginterferon alfa-2a (see section 5.1).

4.3 Contraindications

See peginterferon alfa-2a or interferon alfa-2a prescribing information for contraindications related to either of these products.

- hypersensitivity to ribavirin or to any of the excipients.
- pregnant women (see section 4.4). Copegus must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
- women who are breast-feeding (see section 4.6).
- a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months.
- severe hepatic dysfunction or decompensated cirrhosis of the liver.
- haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia).
- Initiation of peginterferon alfa-2a is 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.

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Copegus combination therapy with peginterferon alfa-2a or interferon alfa-2a, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Copegus and peginterferon alfa-2a or interferon alfa-2a be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions: If treatment with Copegus in combination with peginterferon alfa-2a or interferon alfa-2a is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.

Please refer to the SPC of peginterferon alfa-2a or interferon alfa-2a for further information on special warnings and precautions for use related to either of these products.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie, patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV genotype, age, extrahepatic manifestations, risk of transmission, etc. which influence the decision to treat or not.

Teratogenic risk: See **4.6 Fertility, pregnancy and lactation**. Prior to initiation of treatment with ribavirin 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. For laboratory monitoring of pregnancy please refer to Laboratory tests.

Carcinogenicity: Ribavirin is mutagenic in some *in vivo* and *in vitro* genotoxicity assays. A potential carcinogenic effect of ribavirin cannot be excluded (see section 5.3).

Haemolysis and Cardiovascular system: A decrease in haemoglobin levels to <10 g/dl was observed in up to 15% of patients treated for 48 weeks with Copegus 1000/1200 milligrams in combination with peginterferon alfa-2a and up to 19% of patients in combination with interferon alfa-2a. When Copegus 800 milligram was combined with peginterferon alfa-2a for 24 weeks, 3% of patients had a decrease in haemoglobin levels to <10 g/dl. The risk of developing anaemia is higher in the female population. Although ribavirin has no direct cardiovascular effects, anaemia 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 cardiac disease. Cardiac status must be assessed

before start of therapy and monitored clinically during therapy; if any deterioration occurs, stop therapy (see section 4.2). Patients with a history of congestive heart failure, myocardial infarction, and/or previous or current arrhythmic disorders must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy.

Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of ribavirin and a peginterferon concomitantly with 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 4.5).

The use of Copegus and peginterferon alfa-2a combination therapy in chronic hepatitis C patients who 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 re-treatment.

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.

Liver 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. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued.

Renal impairment: The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of Copegus, preferably by estimating the patient's creatinine clearance. Substantial increases in ribavirin plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine >2 mg/dl or with creatinine clearance <50 ml/minute. There are insufficient data on the safety, efficacy and pharmacokinetics of Copegus in such patients to support specific recommendations for dose adjustments (see section 5.2). Copegus therapy should not be initiated (or continued if renal impairment occurs while on treatment) in such patients, whether or not on haemodialysis, unless it is considered to be essential. Extreme caution is required. Haemoglobin concentrations should be monitored intensively during treatment and corrective action taken as necessary (see section 4.2).

Ocular changes: Copegus is used in combination therapy with alpha interferons. Retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction which may result in loss of vision have been reported in rare instances with combination therapy with alpha interferons. All patients should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination. Patients with preexisting ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during combination therapy with alpha interferons. Combination therapy with alpha interferons should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Transplantation: The safety and efficacy of peginterferon-alfa-2a and Copegus treatment have not been established in patients with liver and other transplantations. Liver and renal graft rejections have been reported with peginterferon-alfa-2a, alone or in combination with Copegus.

HIV/HCV Co-infection: Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with peginterferon alfa-2a with or without ribavirin. In study NR15961, patients concurrently treated with stavudine and interferon therapy with or without ribavirin, the incidence of pancreatitis and/or lactic acidosis was 3% (12/398).

Chronic hepatitis C patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of serious adverse effects (e.g. lactic acidosis; peripheral neuropathy; pancreatitis).

Co-infected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with Copegus in combination with interferons. Baseline variables in co-infected cirrhotic patients that may be associated with hepatic decompensation include: increased serum bilirubin, decreased haemoglobin, increased alkaline phosphatase or decreased platelet count, and treatment with didanosine (ddI). Caution should therefore be exercised when adding peginterferon alfa-2a and Copegus to HAART (see section 4.5).

The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

During treatment co-infected patients should be closely monitored for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function; e.g., Child-Pugh score of 7 or greater). The Child-Pugh scoring may be affected by factors related to treatment (i.e., indirect hyperbilirubinemia, decreased albumin) and not necessarily attributable to hepatic decompensation. Treatment with Copegus in combination with peginterferon alfa-2a or interferon alfa-2a should be discontinued immediately in patients with hepatic decompensation.

Co-administration of Copegus and didanosine is not recommended due to the risk of mitochondrial toxicity (see Section 4.5). Moreover, co-administration of Copegus and stavudine should be avoided to limit the risk of overlapping mitochondrial toxicity.

Laboratory tests: Standard haematologic tests and blood chemistries (complete blood count [CBC] and differential, platelet count, electrolytes, glucose, serum creatinine, liver function tests, uric acid) must be conducted in all patients prior to initiating therapy. 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:

Haemoglobin ≥ 12 g/dl (females); ≥ 13 g/dl (males) Platelets $\geq 90,000/\text{mm}^3$ Neutrophil Count $\geq 1,500/\text{mm}^3$

In patients co-infected with HIV-HCV, limited efficacy and safety data are available in subjects with CD4 counts less than 200 cells/ μL . Caution is therefore warranted in the treatment of patients with low CD4 counts.

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and

periodically thereafter as clinically appropriate.

For women of childbearing potential: Female patients must have a routine pregnancy test performed monthly during treatment and for 4 months thereafter. Female partners of male patients must have a routine pregnancy test performed monthly during treatment and for 7 months thereafter.

Uric acid may increase with Copegus due to haemolysis and therefore predisposed patients should be carefully monitored for development of gout.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Copegus and peginterferon alfa-2a combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Copegus and peginterferon alfa-2a. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

4.5 Interaction 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 alone or concomitantly with interferon alfa-2b or peginterferon alfa-2a.

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 milligrams was decreased by co-administration with an antacid containing magnesium, aluminium and methicone; AUC₀₋₁₂ 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 analogues: 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 viraemia. 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.

Didanosine (ddI): Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased *in vitro* when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactataemia/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 6methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of Copegus and peginterferon alfa-2a concomitantly with azathioprine should be avoided. In individual cases where the benefit of administering Copegus concomitantly with azathioprine warrants the potential risk, it is recommended that close haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped (see section 4.4).

HIV-HCV co-infected patients

No apparent evidence of drug interaction was observed in 47 HIV-HCV co-infected patients who completed a 12 week pharmacokinetic substudy to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine and zidovudine or stavudine). However, due to high variability, the confidence intervals were quite wide. Plasma exposure of ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

4.6 Fertility, pregnancy and lactation

Preclinical data: 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 foetuses and offspring was reduced.

Female patients: Copegus must not be used by women who are pregnant (see section 4.3 and section 4.4). 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 must use a form of effective contraception, during treatment and for 4 months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within 4 months from stopping treatment the patient must be advised of the significant teratogenic risk of ribavirin to the foetus.

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. Either male patients or their female partners of childbearing age must, therefore, be counselled to use a form of effective contraception simultaneously during treatment with Copegus and for 7 months after treatment has been concluded. A pregnancy test must

be performed before therapy is started. Men whose partners are pregnant must be instructed to use a condom to minimise delivery of ribavirin to the partner.

Lactation: It is not known whether ribavirin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Copegus has no or negligible influence on the ability to drive and use machines. However, peginterferon alfa-2a or interferon alfa-2a used in combination with Copegus may have an effect. Please refer to the SPC of peginterferon alfa-2a or interferon alfa-2a for further information.

4.8 Undesirable effects

See peginterferon alfa-2a or interferon alfa-2a prescribing information for additional undesirable effects for either of these products.

Adverse events reported in patients receiving Copegus in combination with interferon alfa-2a are essentially the same as for those reported for Copegus in combination with peginterferon alfa-2a.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Chronic hepatitis C

The most frequently reported adverse events with Copegus in combination with peginterferon alfa-2a 180 micrograms were mostly mild to moderate in severity. Most of them were manageable without the need for discontinuation of therapy.

Chronic hepatitis C in prior non-responder patients

Overall, the safety profile for Copegus in combination with peginterferon alfa-2a in prior nonresponder patients was similar to that in naive patients. In a clinical trial of non-responder patients to prior pegylated interferon alfa-2b/ribavirin, which exposed patients to either 48 or 72 weeks of treatment, the frequency of withdrawal for adverse events or laboratory abnormalities from peginterferon alfa-2a treatment and Copegus treatment was 6% and 7%, respectively, in the 48 week arms and 12% and 13%, respectively, in the 72 week arms. Similarly, for patients with cirrhosis or transition to cirrhosis, the frequencies of withdrawal from peginterferon alfa-2a treatment and Copegus treatment were higher in the 72-week treatment arms (13% and 15%) than in the 48-week arms (6% and 6%). Patients who withdrew from previous therapy with pegylated interferon alfa-2b/ribavirin because of haematological toxicity were excluded from enrolling in this trial.

In another clinical trial, non-responder patients with advanced fibrosis or cirrhosis (Ishak score of 3 to 6) and baseline platelet counts as low as $50,000/\text{mm}^3$ were treated for 48 weeks. Haematologic laboratory abnormalities observed during the first 20 weeks of the trial included anaemia (26% of patients experienced a haemoglobin level of $<10 \text{ g/dl}$), neutropenia (30% experienced an $\text{ANC} < 750/\text{mm}^3$), and thrombocytopenia (13% experienced a platelet count $< 50,000/\text{mm}^3$) (see section 4.4).

Chronic hepatitis C and Human Immunodeficiency Virus Co-infection

In HIV-HCV co-infected patients, the clinical adverse event profiles reported for peginterferon alfa2a, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients. For HIV-HCV patients receiving Copegus and peginterferon alfa-2a combination therapy other undesirable effects have been reported in $\geq 1\%$ to $\leq 2\%$ of patients: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia. Peginterferon alfa-2a treatment was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of peginterferon alfa-2a had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data are available in co-infected patients with CD4+ cell counts $< 200/\mu\text{l}$. (see peginterferon alfa-2a SPC).

Table 5 shows the undesirable effects reported in patients who have received Copegus and peginterferon alfa-2a or interferon alfa-2a therapy.

Table 5 Undesirable Effects Reported with Copegus in combination with Peginterferon alfa-2a for HCV Patients						
Body system	Very Common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1000$ to $< 1/100$	Rare $\geq 1/10,000$ to $< 1/1000$	Very rare $< 1/10,000$	Frequency not known *
Infections and infestations		Upper respiratory tract infection, bronchitis, oral candidiasis, herpes simplex	Lower respiratory tract infection, pneumonia, urinary tract infection, skin infection	Endocarditis, Otitis externa		
Neoplasms benign and malignant			Malignant hepatic neoplasm			
Blood and lymphatic system disorders	Anaemia, Neutropenia	Thrombocytopenia, lymphadenopathy		Pancytopenia	Aplastic anaemia	Pure red cell aplasia
Immune system disorders			Sarcoidosis, thyroiditis	Anaphylaxis, systemic lupus erythematosus, rheumatoid arthritis	Idiopathic or thrombotic thrombocytopenic purpura	Liver and renal graft rejection, Vogt-Koyanagi-Harada disease
Endocrine disorders		Hypothyroidism, hyperthyroidism	Diabetes			
Metabolism and Nutrition Disorders	Anorexia		Dehydration			

Table 5 Undesirable Effects Reported with Copegus in combination with Peginterferon alfa-2a for HCV Patients

Body system	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Very rare <1/10,000	Frequency not known *
Psychiatric disorders	Depression, insomnia	Mood alteration, emotional disorders, anxiety, aggression, nervousness, libido decreased	Suicidal ideation, hallucinations, anger	Suicide, psychotic disorder		Mania, bipolar disorders, homicidal ideation
Nervous system disorders	Headache, dizziness, concentration impaired	Memory impairment, syncope, weakness, migraine, hypo-aesthesia, hyper-aesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence	Peripheral neuropathy	Coma, convulsions, facial palsy		
Eye disorders		Vision blurred, eye pain, eye inflammation, xerophthalmia	Retinal haemorrhage	Optic neuropathy, papilloedema, retinal vascular disorder, retinopathy, corneal ulcer	Vision loss	Serous retinal detachment
Ear and labyrinth disorders		Vertigo, earache	Hearing loss			
Cardiac disorders		Tachycardia, palpitations, oedema peripheral		Myocardial infarction, congestive heart failure, angina, Supraventricular tachycardia arrhythmia, atrial fibrillation, pericarditis		
Vascular disorders		Flushing	Hypertension	Cerebral haemorrhage		

Table 5 Undesirable Effects Reported with Copegus in combination with Peginterferon alfa-2a for HCV Patients

Body system	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Very rare <1/10,000	Frequency not known *
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough	Dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, nasal congestion, rhinitis, sore throat	Wheezing	Interstitial pneumonitis with fatal outcome, pulmonary embolism		
Gastrointestinal disorders	Diarrhoea, nausea, abdominal pain	Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, constipation, dry mouth	Gastrointestinal bleeding, cheilitis, gingivitis	Peptic ulcer, pancreatitis		<u>ischemic colitis</u> , <u>ulcerative colitis</u>
Hepatobiliary disorders			Hepatic dysfunction	Hepatic failure, cholangitis, fatty liver		
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, pruritus, dry skin	Rash, sweating increased, psoriasis, urticaria, eczema, skin disorder, photosensitivity reaction, night sweats			Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps		Myositis		Rhabdomyolysis
Renal and Urinary Disorders						Renal failure, nephrotic syndrome
Reproductive system and breast disorders		Impotence				

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Table 5 Undesirable Effects Reported with Copegus in combination with Peginterferon alfa-2a for HCV Patients						
Body system	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Very rare <1/10,000	Frequency not known *
General disorders and administration site conditions	Pyrexia, rigors, pain, asthenia, fatigue, injection site reaction, irritability	Chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst				
Investigations		Weight decreased				
Injury and poisoning				Substance overdose		

* Identified in postmarketing experience

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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 4.2). With peginterferon alfa-2a and Copegus combination treatment, up to 2% of patients experienced increased ALT levels that led to dose modification or discontinuation of treatment.

Haemolysis is the dose limiting toxicity of ribavirin therapy. A decrease in haemoglobin levels to <10 g/dl was observed in up to 15% of patients treated for 48 weeks with Copegus 1000/1200 milligrams in combination with peginterferon alfa-2a and up to 19% of patients in combination with interferon alfa-2a. When Copegus 800 milligram was combined with peginterferon alfa-2a for 24 weeks, 3% of patients had a decrease in haemoglobin levels to <10 g/dl. In most cases the decrease in haemoglobin occurred early in the treatment period and stabilised concurrently with a compensatory increase in reticulocytes.

Most cases of anaemia, leucopenia and thrombocytopenia were mild (WHO grade 1). WHO grade 2 laboratory changes were reported for haemoglobin (4% of patients), leucocytes (24% of patients) and thrombocytes (2% of patients). Moderate (absolute neutrophil count (ANC): 0.749-0.5x10⁹/L) and severe (ANC: <0.5x10⁹/L) neutropenia was observed in 24% (216/887) and 5% (41/887) of patients receiving 48 weeks of Copegus 1000/1200 milligrams in combination with peginterferon alfa-2a.

An increase in uric acid and indirect bilirubin values associated with haemolysis were observed in some patients treated with Copegus used in combination with peginterferon alfa-2a or interferon alfa-2a and values returned to baseline levels within 4 weeks after the end of therapy. In rare cases (2/755) this was associated with clinical manifestation (acute gout).

Laboratory values for HIV-HCV co-infected patients

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia 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/mm³ was observed in 13% and 11% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm³ was observed in 10% and 8% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Anaemia (haemoglobin < 10g/dL) was reported in

7% and 14% of patients treated with peginterferon alfa-2a monotherapy or in combination therapy, respectively.

4.9 Overdose

No cases of overdose of Copegus have been reported in clinical trials. Hypocalcaemia and hypomagnesaemia have been observed in persons administered dosages greater than four times the maximal recommended dosages. In many of these instances ribavirin was administered intravenously. Due to the large volume of distribution of ribavirin, significant amounts of ribavirin are not effectively removed by hemodialysis.