Copegus®

Ribavirin

Direct acting antiviral

1. PHARMACEUTICAL FORM

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

Light pink, oval-shaped film-coated tablets (marked with RIB 200 on one side and ROCHE on the opposite side).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Ribavirin.

3. CLINICAL PARTICULARS

3.1 Therapeutic Indications

The combination of Copegus with peginterferon alfa 2a or interferon alfa 2a is indicated in adult patients with elevated transaminase who are positive for serum HCV RNA, including patients with compensated cirrhosis. The combination of Copegus with peginterferon alfa 2a is also indicated in adult patients without elevated transaminase who are positive for serum HCV RNA, including patients with compensated cirrhosis (see section 3.4).

The combination with peginterferon alfa 2a is also indicated in patients with HIV disease that is clinically stable (e.g. antiretroviral therapy not required or receiving stable antiretroviral therapy), including patients with compensated cirrhosis (see section 3.3). The combination regimens are indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped.

Copegus is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa-2a or with interferon alfa-2a. Copegus monotherapy must not be used.

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

3.2 Dosage and Method of Administration

3.2.1 Standard Dosage

Copegus film-coated tablets are administered orally in two divided doses with food (morning and evening), in combination with interferon alfa and peginterferon alfa solution for injection.

The exact dose and duration of treatment depend on the interferon product used.

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 regardless of viral load should receive 48 weeks of therapy. Patients infected with HCV genotype 2/3 regardless of viral load should receive 24 weeks of therapy (see Table 1).

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

Genotype	Daily Copegus Dose	Duration of treatment	Number of 200 mg tablets
Genotype 1	<75 kg = 1,000 mg	48 weeks	5 (2 morning, 3 evening)
	≥75 kg = 1,200 mg	48 weeks	6 (3 morning, 3 evening)
Genotype 2/3	800 mg	24 weeks	4 (2 morning, 2 evening)

In general, patients infected with genotype 4 are considered hard to treat and limited study data (N=49) are compatible with a posology as for genotype 1. When deciding on the duration of therapy, the presence of additional factors should also be considered. For patients infected with genotype 5 or 6, this posology should also be considered.

HIV-HCV Co-infection
The recommended dosage for Copegus in combination with 180 micrograms once weekly of peginterferon alfa-2a is 800 milligrams, daily for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with ribavirin doses greater than 800 milligrams daily or a duration of therapy less than 48 weeks has not been studied.

Predictability of response and non-response
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)
enotype 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.

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). The use of Copegus in combination with interferon alfa-2a in patients with normal ALT levels at baseline have not been studied in any clinical trials.

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)

Please refer to the package insert of interferon alfa or peginterferon alfa products for further information on dosing and duration of treatment.

3.2.2 Special Dosage Instructions

Dosage modification for adverse reactions
If severe adverse reactions or laboratory abnormalities develop during therapy with Copegus modify the dosages until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Dosage Modification Guidelines, Table 4*).

Copegus should be administered with caution to patients with existing cardiac disease. Because of the recognised hemolysis associated with ribavirin therapy, separate guidelines are provided for patients with a history of cardiovascular disease. In these patients, a permanent dose reduction of Copegus is required if the hemoglobin decreases by >2 g/dl during any 4-week period. In addition, if the hemoglobin remains <12g/dl after 4 weeks on a reduced dose, discontinue Copegus. If there is any deterioration of cardiovascular status, therapy should be stopped.

Table 4 Dosage Modification Guidelines

Laboratory Values	Reduce Copegus dose to 600 mg/day* only if:	Discontinue Copegus if **:
Hemoglobin	<10 g/dl	<8.5g/dl
Hemoglobin: Patients with History of Stable cardiac disease	>2g/dl decrease in hemoglobin during any 4 week period during treatment (permanent dose reduction)	<12g/dl after 4 weeks of dose reduction

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

If intolerance persists after Copegus dose adjustment, discontinuation of the drug may be necessary.

Specific recommendations for management of treatment-emergent anemia are as follows: Copegus should be reduced to 600 mg/day (200mg in the morning and 400mg in the evening) if either of the following apply: a patient without significant cardiovascular disease experiences a fall in hemoglobin to <10g/dl and ≥8.5g/dl, or a patient with stable cardiovascular disease experiences a fall in hemoglobin by ≥2g/dl during any four weeks of treatment. A return to original dosing is not recommended. Copegus should be discontinued if either of the following apply: a patient without significant cardiovascular disease experiences a fall in hemoglobin confirmed to <8.5g/dl. A patient with stable cardiovascular disease maintains a hemoglobin value <12g/dl despite 4 weeks on a reduced dose. If the abnormality is reversed, ribavirin may be restarted at 600mg daily, and further increased to 800mg daily at the discretion of the treating physician. However, a return to original dosing is not recommended.

Use in renal impairment:
Standard dose regimens (adjusted by the body weight cut off 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

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.

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.

Use in hepatic impairment: No pharmacokinetic interaction appears between ribavirin and hepatic function. Therefore, no dose adjustment of Copegus is required in patients with hepatic impairment.

Use in the elderly (≥65 years of age): 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: Safety and effectiveness of ribavirin in combination with interferon alfa and peginterferon alfa in these patients have not been evaluated. Treatment with Copegus is not recommended for use in children and adolescents under the age of 18.

Dosage modification for patients receiving chronic hemodialysis: In renally impaired patients receiving chronic hemodialysis, Copegus can be safely administered at a dose of 200 mg daily.

Please refer to the package insert of interferon alfa or peginterferon alfa products for additional information.

3.3 Contraindications

Copegus is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. It is also contraindicated in the following:

- Patients with hemoglobinopathies (e.g. thalassemia, sickle-cell anemia)
- Patients with significant or unstable cardiac disease
- Patients with autoimmune hepatitis
- Patients with severe hepatic dysfunction or decompensated cirrhosis of the liver.

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

- Women who are pregnant. Women of childbearing age should not be on Copegus until pregnancy is excluded.
- Men whose female partners are pregnant.
- Women who are breastfeeding.

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

3.4 Special Warnings and Special Precautions for Use

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

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.

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.

Teratogenic risk (see 3.6 Pregnancy and Lactation)
Copegus may cause birth defects and/or death of the unborn child.

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 increases with escalation of the ribavirin dose (see section 3.6).

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 continous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during treatment with ribavirin.

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.

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 3.2**).** 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 (marked decreases in RBCs, 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 reversed within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone.

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.

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.

Psychiatric and Central Nervous System (CNS)
Patients with existence of severe psychiatric conditions:

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

Severe CNS effects, particularly depression, suicidal ideation and suicide have been observed in some patients during Copegus combination therapy with peginterferon alfa-2a or interferon alfa-2a. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with interferon alfa-2a. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that patients be carefully monitored by the prescribing physician. If such symptoms appear, the potential seriousness of these undesirable effects

must be borne in mind by the prescribing physician. If symptoms persist or worsen, discontinue both Copegus and peginterferon alfa-2a or interferon alfa-2a.

Renal
The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients (see section 3.2.2 and 4.2.5). 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 3.2.2). 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 3.2.2 and section 4.2.2).

In a study of patients with end-stage renal disease (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 3.2.2 and section 4.2.2).
Patients with creatinine clearance less than or equal to 50 mL/min receiving Copegus should be carefully monitored.

Please refer to the package insert of interferon alfa or peginterferon alfa products for additional information.

HIV/HCV Co-infection
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 (ddl). Caution should therefore be exercised when adding peginterferon alfa-2a and Copegus to HAART therapy (see section 3.5). Co-infected patients should be closely monitored, assessing their Child-Pugh score during treatment and should be immediately discontinued if they progress to a Child-Pugh score of 7 or greater.

Patients treated with Copegus and alpha interferon (standard and pegylated) combination therapy and zidovudine could be at increased risk of developing anaemia.

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. 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:

Hemoglobin	≥ 12g/dl (females); ≥ 13g/dl (males)
Platelets	≥ 90,000/mm^3
Neutrophil Count	≥ 1,500/mm^3

In patients co-infected with HIV-HCV limited efficacy and safety data (N=51) 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.

After initiation of Copegus therapy, hematological tests should be performed at 2 and 4 weeks and biochemical tests should be performed at 4 weeks. These laboratory tests should be performed periodically during treatment as clinically appropriate. For women with childbearing potential, monthly pregnancy testing should be done during therapy and for 6 months thereafter.

Any patient developing significant liver function abnormalities must be monitored closely. Copegus must be discontinued if signs and symptoms progress.

Please refer to the package insert of interferon alfa or peginterferon alfa products for additional information.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
The carcinogenic potential of ribavirin has not been fully determined. In a p53 (+/-) mouse carcinogenicity study at doses up to the maximum tolerated dose of 100 mg/kg/day, ribavirin was not oncogenic. However, on a body surface area basis, this dose was 0.5 times the maximum recommended human 24-hour dose of ribavirin. A study to assess the carcinogenic potential of ribavirin in rats is ongoing.

Mutagenesis
Ribavirin demonstrated mutagenic activity in the in vitro mouse lymphoma assay. No clastogenic activity was observed in an in vivo mouse micronucleus assay at doses up to 2000 mg/kg. However, results from studies published in the literature show clastogenic activity in the in vivo mouse micronucleus assay at oral doses up to 2000 mg/kg. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. However, potential carcinogenic risk to humans cannot be excluded.

Impairment of Fertility
In a fertility study in rats, ribavirin showed a marginal reduction in sperm counts at the dose of 100 mg/kg/day with no effect on fertility. Upon cessation of treatment, total recovery occurred after 1 spermatogenesis cycle. Abnormalities in sperm were observed in studies in mice designed to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (approximately 0.1-0.8 times the maximum recommended human 24-hour dose of ribavirin) administered for 3 to 6 months. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenic cycles.

Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive COPEGUS unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months posttherapy (ie, 15 half-lives of clearance for ribavirin).

No reproductive toxicology studies have been performed using PEGASYS in combination with COPEGUS. However, peginterferon alfa-2a and ribavirin when administered separately, each has adverse effects on reproduction. It should be assumed that the effects produced by either agent alone would also be caused by the combination of the two agents.

3.5 Interactions with other Medical Products and other Forms of Interaction
Interaction studies have been conducted with ribavirin, interferon alfa, pegylated interferon alfa and antacids. Ribavirin concentrations are similar when given concomitantly with interferon alfa or peginterferon alfa 2a. Ribavirin concentrations are similar when given as monotherapy or in combination with 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 600mg was decreased by co-administration with an antacid containing magnesium, aluminium and methicone; AUCtf 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 viraemia or an increase in adverse reactions. Plasma pharmacokinetics of ddI were not significantly affected by concomitant ribavirin, 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.

Stavudine and Zidovudine: 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 ribavirin 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 ribavirin concurrently with either of these two agents. If HIV RNA levels increase the use of ribavirin concomitantly with reverse transcriptase inhibitors must be reviewed.

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

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.

3.6 Pregnancy and Lactation
Copegus must not be used by women who 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.

Female patients: 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.

Lactation: 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.

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.

3.7 Effects on Ability to Drive and Use Machines
Copegus has no or negligible influence on the ability to drive or operating machinery; however, interferon alfa or peginterferon alfa 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.

3.8 Undesirable Effects
3.8.1 Experience from Clinical Trials
The types and frequency of adverse events with combination therapy are consistent with the known safety profile of interferon alfa or peg interferon alfa 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%).

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=31) 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 800mg, 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
	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
Body System	%	%	%
Metabolism & nutrition disorders			
Anorexia	20%	27%	23%
Weight decrease	2%	7%	16%
Psychiatric disorders			
Insomnia	30%	32%	19%
Irritability	28%	24%	15%
Depression	17%	21%	22%
Concentration impairment	8%	10%	2%
Nervous system disorders			
Headache	48%	47%	35%
Dizziness	13%	15%	7%
Respiratory, thoracic and mediastinal disorders			
Dyspnea	11%	13%	7%
Cough	8%	13%	3%
Gastrointestinal disorders			
Nausea	29%	28%	24%
Diarrhea	15%	14%	16%
Abdominal pain	9%	10%	7%
Skin and subcutaneous tissue disorders			
Alopecia	25%	24%	10%
Pruritus	25%	21%	5%
Dermatitis	15%	16%	1%
Dry skin	13%	12%	4%
Musculoskeletal, connective tissue and bone disorders			
Myalgia	42%	38%	32%
Arthralgia	20%	22%	16%
General disorders and administration site conditions			
Fatigue	45%	49%	40%
Pyrexia	37%	39%	41%
Rigors	30%	25%	16%

	HCV		HIV-HCV
	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
Injection site reaction	28%	21%	10%
Asthenia	18%	15%	26%
Pain	9%	10%	6%

Table 7 Adverse Reactions occurring in ≥ 10% of Hepatitis C patients with normal ALT levels

	PEGASYS 180 µg with COPEGUS 800 mg 24 weeks (n=212) %	PEGASYS 180 µg with COPEGUS 800 mg 48 weeks (n=210) %	Untreated Control 48 weeks (n=69) %
General disorders			
Fatigue	51	51	17
Pyrexia	30	43	3
Rigors	24	25	1
Asthenia	22	23	10
Injection site reaction	16	16	-
Decreased appetite	8	16	1
Back pain	9	10	9
Psychiatric disorders			
Insomnia	35	36	7
Depression	26	27	6
Irritability	27	26	1
Anxiety	10	8	3
Musculoskeletal, connective tissue and bone disorders			
Myalgia	38	44	7
Arthralgia	32	30	4
Nervous system disorders			
Headache	44	56	7
Dizziness	89	17	1
Skin and subcutaneous tissue disorders			
Alopecia	20	28	-
Pruritus	16	20	1
Rash	14	16	-
Dermatitis			
Dry skin	11	9	-
Gastrointestinal disorders			
Nausea	32	40	1
Diarrhoea	19	26	4
Vomiting	12	13	3
Upper abdominal pain	9	12	7
Dyspepsia	9	10	-
Respiratory, thoracic and mediastinal disorders			
Cough	14	19	1
Dyspnoea	14	15	-
Pharyngitis	9	10	4
Metabolism and nutrition disorders			
Anorexia	16	13	1

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: 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, oedema 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 alfa 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 3.2.2).

Haemolysis is the defining 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 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 haemoglobin 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 stabilised 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/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. Anemia (hemoglobin < 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.

3.8.2 Post Marketing

During the post-marketing period, erythema multiforme, Stevens 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.

3.9 Overdose

No cases of overdose of Copegus have been reported in clinical trials. Hypocalcemia and hypomagnesemia have been observed in persons administererd 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.

4. PHARMACOLOGICAL PROPERTIES & EFFECTS

4.1 Pharmacodynamic Properties

4.1.1 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 interferon alfa or peginterferon alfa 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.

4.1.2 Efficacy / Clinical Studies

Chronic Hepatitis C

Study results

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 8).

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

HCV patients with normal ALT

In study NR16071, HCV patients with normal ALT values were randomized to receive peginterferon alfa-2a 180 micrograms/week with a Copegus dose of 800 milligrams/day for either 24 or 48 weeks regardless of HCV genotype, followed by a 24 week treatment free follow-up period or an untreated control group for 72 weeks. (see Table 9 and Table 10 for the SVRs reported in the treatment arms of this study as compared to corresponding treatment arms from study NV15942).

Table 10 Sustained Virological Response based on Genotype and Viral Load after Copegus Combination Therapy with Pegasys in HCV Patients with Normal ALT Levels

	Copegus 800mg & **Pegasys** 180mcg 24 weeks	**Copegus** 800mg & **Pegasys** 180mcg 48 weeks
All patients	30% (63/212)	52% (109/210)
Genotype 1	13% (19/144)	40% (57/141)
Low viral load	16% (14/87)	47% (42/89)
High viral load	9% (5/55)	27% (14/51)
Genotype 2-3	72% (42/58)	78% (46/59)
Low viral load	80% (24/30)	81% (25/31)
High viral load	64% (18/25)	75% (21/28)

There were no actual studies conducted in patients with normal ALT values using Copegus dose of 1000 or 1200 milligrams/day.

HIV-HCV Co-infection

In study NR15961, 860 HIV-HCV co-infected patients were randomized and treated with peginterferon alfa-2a 180mcg/week and placebo, peginterferon alfa-2a 180mcg/week and ribavirin 800mg/day or interferon alfa-2a 3 MIU three times weekly and ribavirin 800mg/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 11.

Table 11 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 180mcg, Copegus 800mg vs. Interferon alfa-2a 3MIU Copegus 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), p-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

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

Ribavirin 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.

4.2 Pharmacokinetic Properties

4.2.1 Absorption

Ribavirin is absorbed rapidly following oral administration of a single dose (mean T_{max} = 1.5 hours). Absorption is extensive with approximately 10% of a radio-labelled 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 - 1200mg of 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 600mg dose Copegus was increased by coadministration of a high fat meal. The ribavirin exposure parameters of $AUC_{(0\text{-}192h)}$ 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 or interferon alfa-2b and ribavirin. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food.

4.2.2 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.

4.2.3 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.

4.2.4 Elimination

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

4.2.5 Pharmacokinetics in Special Populations

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. 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 3.2.2). 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 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 interferon alfa or peginterferon alfa is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

4.2.6 Preclinical Safety

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 increases with escalation of the ribavirin dose. Survival of fetuses and offspring is reduced.

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.

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.

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.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, maize starch, magnesium stearate, ethyl cellulose, hydroxypropyl methylcellulose, titanium dioxide (E171), talc, iron oxide yellow (E172), iron oxide red (E172), triacetin.

5.2 Incompatibilities

In absence of incompatibility studies Copegus must not be mixed with other medicinal products.

5.3 Stability

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

See also outer pack for storage remark.

5.4 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.

6. PACKS

Film-coated tablets 42, 168

Medicine: keep out of reach of children

Roche

Current at Jul 2015

Product owner: F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland