

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Copegus 200 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 milligrams of ribavirin.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet

*Product imported from the UK:*

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

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.

The combination of Copegus with peginterferon alfa-2a or interferon alfa-2a is indicated in adult patients with elevated transaminases and who are positive for serum HCV-RNA, including patients with compensated cirrhosis (See section 4.4). The combination with peginterferon alfa-2a is also indicated in patients co-infected with clinically stable HIV, including patients with compensated cirrhosis (See section 4.3). 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.

Please refer to the Summary of Product Characteristics (SPC) of peginterferon alfa-2a or interferon alfa-2a for prescribing information particular to either of these products.

### 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 tablets are administered orally in two divided doses with food (morning and evening). The tablets should not be broken or crushed. Since ribavirin is considered a potential teratogen, caution should be observed in handling broken tablets.

#### 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 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 for HCV patients**

Genotype	Daily Copegus Dose	Duration of treatment	Number of 200mg 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=66) 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	<b>95%</b> (97/102)	467	271	<b>58%</b> (271/467)
Genotype 2 and 3 (N=96)	3	3	<b>100%</b> (3/3)	93	81	<b>87%</b> (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).

**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 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 and efficacy of ribavirin in patients with serum creatinine > 2 mg/dl or creatinine clearance < 50 ml/min, whether or not on haemodialysis, to support recommendations for dose adjustments. 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 **4.4 Special warnings and special precautions for use and see 5.2 Pharmacokinetic properties**).

**Use in hepatic impairment:** No pharmacokinetic interaction appears between ribavirin and hepatic function (see **5.2 Pharmacokinetic properties**). 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:** Safety and effectiveness of ribavirin in combination with peginterferon alfa-2a and interferon alfa-2a in these patients have not been fully evaluated. Treatment with Copegus is not recommended for use in children and adolescents under the age of 18.

### 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 4.4 Special warnings and special precautions for use**). 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 4.6 Pregnancy and lactation**).
- 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 less than or equal to 6 (Please refer to the SPC of peginterferon alfa-2a for Child-Pugh assessment).

### 4.4 Special warnings and precautions for use

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.

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

#### **Teratogenic risk: See 4.6 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.

**Carcinogenicity:** Ribavirin is mutagenic in some in vivo and in vitro genotoxicity assays.

A potential carcinogenic effect of ribavirin cannot be excluded (see 5.3 Preclinical safety data).

**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 4.2 Posology and method of administration). 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.

**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.

**Psychiatric and Central Nervous System (CNS):**

Patients with existence of history 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 individualised 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 impairment:** The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients (see 5.2 Pharmacokinetic properties). 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 and efficacy of Copegus in such patients to support recommendations for dose adjustments. 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 4.2. Posology and method of administration and see 5.2 Pharmacokinetic properties).

**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 therapy. (see 4.5 Interaction with other medicinal products and other forms of interaction).

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.

**Laboratory tests:** Standard haematologic 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:

Haemoglobin  $\geq 12$  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 (N=51) are available in subjects with CD4 counts less than 200 cells/ $\mu\text{L}$ . 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 6 months thereafter. Female partners of male patients must have a routine pregnancy test performed monthly during treatment and for 6 months thereafter.

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

#### **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; AUC<sub>0-t</sub> 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 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):** 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 in this study, although intracellular ddATP was not measured.

### **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).

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.

## **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 4.3 Contraindications and see 4.4 **Special warnings and special precautions for use**). 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 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. Male patients and their female partners of childbearing age must, therefore, be counselled to use 2 forms of effective contraception simultaneously during treatment with Copegus and for 6 months after treatment has been concluded. Women must have a negative pregnancy test 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; however, peginterferon alfa-2a or interferon alfa-2a used in combination may have an effect. Thus, patients who develop fatigue, somnolence, or confusion during treatment must be cautioned to avoid driving or operating machinery.

## 4.8 Undesirable effects

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

The most frequently reported adverse reactions with Copegus in combination with peginterferon alfa-2a 180 micrograms were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy.

### **HIV-HCV co-infected patients**

In HIV-HCV co-infected patients, the clinical adverse event profiles reported for peginterferon alfa-2a, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients. 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 (N = 31) are available in co-infected patients with CD4+ cell counts < 200/ $\mu$ l. (see peginterferon alfa-2a SPC).

Table 5 summarises the safety overview of different treatment regimens of Copegus in combination with peginterferon alfa-2a for HCV and HIV-HCV patients.

<b>Table 5. Safety Overview of Copegus Treatment Regimens in Combination with Peginterferon alfa-2a for HCV and HIV-HCV patients</b>			
	<b>HCV mono- infection</b>	<b>HCV mono- infection</b>	<b>HIV-HCV co- Infection</b>
	<b>Copegus 800 mg</b>	<b>Copegus 1000/1200 mg</b>	<b>Copegus 800 mg</b>
	24 weeks	48 weeks	48 weeks
	&	&	&
	<b>PEG-IFN alfa-2a 180 mcg</b>	<b>PEG-IFN alfa-2a 180 mcg</b>	<b>PEG-INF alfa-2a 180 mcg</b>
Serious adverse events	3%	11%	17%
Anaemia (haemoglobin < 10g/dl)	3%	15%	14%
Ribavirin dose modification	19%	39%	37%
Premature withdrawals due to adverse events	4%	10%	12%
Premature withdrawals due to laboratory abnormalities	1%	3%	3%

Table 6 shows the most common undesirable effects reported in 10% of patients who have received Copegus and peginterferon alfa-2a or interferon alfa-2a therapy.



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. Table 6: Adverse Reactions (10 % Incidence in Any Treatment Group) for HCV and HIV-HCV patients

<b>Table 6: Adverse Reactions (≥10 % Incidence in Any Treatment Group) for HCV and HIV-HCV patients</b>			
	<b>HCV</b>	<b>HCV</b>	<b>HIV-HCV</b>
	Copegus	Copegus	Copegus
	800 mg	1,000 or 1,200 mg	800 mg
	&	&	&
	Peginterferon	Peginterferon	Peginterferon
	alfa-2a	alfa-2a	Alfa-2a
	180 micrograms	180 micrograms	180 micrograms
	(NV15942)	(NV15801 + NV15942)	(NR15961)
	24 weeks	48 weeks	48 weeks
	N=207	N=887	N=288
<b>Body System</b>	%	%	%
<b>Metabolism &amp; Nutrition disorders</b>			
Anorexia	20 %	27 %	23%
Weight Decrease	2%	7%	16%
<b>Psychiatric Disorders</b>			
Insomnia	30 %	32 %	19%
Irritability	28 %	24 %	15%
Depression	17 %	21 %	22%
Concentration Impairment	8 %	10 %	2%
<b>Nervous system disorders</b>			
Headache	48 %	47 %	35%
Dizziness	13 %	15 %	7%
<b>Respiratory, thoracic and mediastinal disorders</b>			
Dyspnoea	11 %	13 %	7%
Cough	8 %	13 %	3%
<b>Gastrointestinal Disorders</b>			
Nausea	29 %	28 %	24%
Diarrhoea	15 %	14 %	16%
Abdominal Pain	9 %	10 %	7%
<b>Skin and subcutaneous tissue disorders</b>			

Alopecia	25 %	24 %	10%
Pruritus	25 %	21 %	5%
Dermatitis	15 %	16 %	1%
Dry skin	13 %	12 %	4%
<b>Musculoskeletal, connective tissue and bone disorders</b>			
Myalgia	42 %	38 %	32%
Arthralgia	20 %	22 %	16%
<b>General disorders and administration site conditions</b>			
Fatigue	45 %	49 %	40%
Pyrexia	37 %	39 %	41%
Rigors	30 %	25 %	16%
Asthenia	18 %	15 %	26%
Pain	9 %	10 %	6%
Injection Site Reaction	28 %	21 %	

Undesirable effects reported in <10% patients on Copegus in combination with peginterferon alfa-2a or Copegus in combination with interferon alfa-2a are reported in table 7.

**Table 7. Undesirable Effects ( <10% Incidence) Reported for HCV and HIV-HCV patients**

<b>Body system</b>	<b>Common &lt;10% - 5%</b>	<b>Common &lt;5% -1%</b>	<b>Uncommon to Rare serious adverse events &lt;1% - &lt;0.1%</b>
Infections and infestations		herpes simplex, URI infection, bronchitis, oral candidiasis	Skin infection, lower respiratory tract infection, otitis externa, endocarditis Hepatic neoplasm
Neoplasms benign and malignant			
Blood and lymphatic system disorders		Anaemia, lymphadenopathy, thrombocytopenia	
Immune system disorders			ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE, sarcoidosis, anaphylaxis Diabetes
Endocrine disorders		Hypothyroidism, hyperthyroidism	
Psychiatric disorders	mood alteration, emotional disorders, anxiety	Nervousness, libido decreased, aggression	Suicide ideation, suicide, anger
Nervous system disorders	memory impairment	taste disturbance, weakness, paraesthesia, hypoaesthesia, tremor, migraine, somnolence, hyperaesthesia, nightmares, syncope	Peripheral neuropathy, coma
Eye disorders		vision blurred, eye inflammation, xerophthalmia, eye pain	Corneal ulcer, retinopathy, retinal vascular disorder, retinal haemorrhage, papilloedema, optic neuropathy, vision loss
Ear and labyrinth disorders		vertigo, earache	
Cardiac disorders		Palpitations, oedema peripheral, tachycardia	Arrhythmia, supraventricular tachycardia, atrial fibrillation, CHF, angina, myocardial infarction, pericarditis
Vascular disorders		Flushing	Cerebral haemorrhage, hypertension
Respiratory, thoracic and mediastinal disorders		sore throat, dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, rhinitis, nasal congestion	Bronchoconstriction, interstitial pneumonitis with fatal outcome, pulmonary embolism

Gastrointestinal disorders	vomiting, dry mouth, dyspepsia	mouth ulceration, flatulence, gingival bleeding, stomatitis, dysphagia, glossitis	Peptic ulcer, gastrointestinal bleeding, reversible pancreatic reaction (ie, amylase/lipase increase with or without abdominal pain)
Hepato-biliary disorders			Hepatic failure, hepatic dysfunction, fatty liver, cholangitis
Skin and subcutaneous tissue disorders	rash, sweating increased	Eczema, night sweats, psoriasis, photosensitivity reaction, urticaria, skin disorder	Angioedema
Musculoskeletal, connective tissue and bone disorders	Back pain	Muscle cramps, neck pain, musculoskeletal pain, bone pain, arthritis, muscle weakness	Myositis
Reproductive system and breast disorders		Impotence	
General disorders and administration site conditions		Malaise, lethargy, chest pain, hot flushes, thirst, influenza like illness	
Injury and poisoning			Substance overdose

Very rarely, alpha interferons including peginterferon alfa-2a, used in combination with Copegus, may be associated with pancytopenia including aplastic anaemia.

For HIV-HCV patients receiving Copegus and peginterferon alfa-2a combination therapy, other undesirable effects have been reported in 1% to 2% of patients: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

**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 **4.2 Posology and method of administration, Dosage Modification Guidelines**). 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 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 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. It is not expected that patients will need to discontinue therapy because of decrease in haemoglobin levels alone. 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, leukopenia and thrombocytopenia were mild (WHO grade 1). WHO grade 2 laboratory changes was reported for haemoglobin (4% of patients), leucocytes (24% of patients) and thrombocytes (2% of patients). Moderate (absolute neutrophil count (ANC): 0.749-0.5x10<sup>9</sup>/L) and severe (ANC: <0.5x10<sup>9</sup>/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/mm<sup>3</sup> was observed in 13% and 11% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm<sup>3</sup> 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. Ribavirin is not effectively removed by haemodialysis.

**5 PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Direct acting antivirals, nucleosides and nucleotides (excl. reverse transcriptase inhibitors), ATC code: J05A B04.

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 peginterferon alfa-2a or interferon alfa-2a exerts its effects against HCV is unknown.

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received treatment with 180 micrograms peginterferon alfa-2a. The first phase of decline occurs 24 to 36 hours after the first dose of peginterferon alfa-2a and is followed by the second phase of decline which continues over the next 4 to 16 weeks in patients who achieve a sustained response.

Copegus had no significant effect on the initial viral kinetics over the first 4 to 6 weeks in patients treated with the combination of Copegus and pegylated interferon alfa-2a or interferon alfa.

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.

**Clinical Trial Results****Copegus in combination with peginterferon alfa-2a****Predictability of response**

Please refer to section **4.2 Posology and method of administration, in Table 2.**

**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. Only HIV-HCV co-infected patients were included in the study NR15961 (see Table 10). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/μl.

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 either the combination of interferon alfa-2b and ribavirin or peginterferon alfa-2a monotherapy.

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).

For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see tables 8, 9 and 10, respectively. 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)

	<b>Study NV15942</b>	<b>Study NV15801</b>	
	Copegus	Copegus	Ribavirin
	1,000/1,200 mg	1,000/1,200 mg	1,000/1,200 mg
	&	&	&
	Peginterferon alfa-2a	Peginterferon alfa-2a	Interferon alfa-2b
	180 micrograms	180 micrograms	3 MIU
	(N=436)	(N=453)	(N=444)
Response at End of Treatment	48 weeks 68%	48 weeks 69%	48 weeks 52%
Overall Sustained Response	63%	54%*	45%*
*95% CI for difference: 3% to 16% p-value (stratified Cochran-Mantel-Haenszel test) = 0.003			

The virological responses of patients treated with Copegus and peginterferon alfa-2a combination therapy in relation to genotype and viral load are summarised in table 9 for HCV monoinfected patients and 10 for HIV-HCV co-infected patients respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype (see table 1).

The difference between treatment regimens was in general not influenced by viral load or presence/absence of cirrhosis; therefore treatment recommendations for genotype 1, 2 or 3 are independent of these baseline characteristics.

**Table 9. Sustained Virological Response based on Genotype and Viral Load after Copegus Combination Therapy with peginterferon alfa-2a**

	<b>Study NV15942</b>				<b>Study NV15801</b>	
	<b>Copegus</b>	<b>Copegus</b>	<b>Copegus</b>	<b>Copegus</b>	<b>Copegus</b>	<b>Ribavirin</b>
	800 mg	1000/1200 mg	800 mg	1000/1200 mg	1000/1200 mg	1000/1200 mg
	&	&	&	&	&	&
	<b>PEG-IFN</b>	<b>PEG-IFN</b>	<b>PEG-IFN</b>	<b>PEG-IFN</b>	<b>PEG-IFN</b>	<b>Interferon</b>
	<b>alfa-2a</b>	<b>alfa-2a</b>	<b>alfa-2a</b>	<b>alfa-2a</b>	<b>alfa-2a</b>	<b>alfa-2b</b>
	180 mcg	180 mcg	180 mcg	180 mcg	180 mcg	3 MIU
	24 weeks	24 weeks	48 weeks	48 weeks	48 weeks	48 weeks
<b>Genotype 1</b>	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)

<b>Genotype 2/3</b>	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)
<b>Genotype 4</b>	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 randomised to receive peginterferon alfa-2a 180 micrograms/week with a Copegus dose of 800 milligrams/day for either 24 or 48 weeks followed by a 24 week treatment free follow-up period or an untreated control group for 72 weeks. The SVRs reported in the treatment arms of this study were similar to the corresponding treatment arms from study NV15942.

**HIV-HCV co-infected patients**

**Table 10 Sustained Virological Response based on Genotype and Viral Load after Copegus Combination Therapy with peginterferon alfa-2a in HIV-HCV co-infected patients**

Study NR15961

	<b>Interferon alfa-2a</b>	<b>Peginterferon alfa-2a</b>	<b>Peginterferon alfa-2a</b>
	3 MIU	180 mcg	180 mcg
	&	&	&
	<b>Copegus 800 mg</b>	<b>Placebo</b>	<b>Copegus 800 mg</b>
	48 weeks	48 weeks	48 weeks
<b>All patients</b>	12% (33/285)*	20% (58/286)*	40% (116/289)*
<b>Genotype 1</b>	7% (12/171)	14% (24/175)	29% (51/176)
Low viral load	19% (8/42)	38% (17/45)	61% (28/46)
High viral load	3% (4/129)	5% (7/130)	18% (23/130)
<b>Genotype 2-3</b>	20% (18/89)	36% (32/90)	62% (59/95)
Low viral load	27% (8/30)	38% (9/24)	61% (17/28)
High viral load	17% (10/59)	35% (23/66)	63% (42/67)

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

\* peginterferon alfa-2a 180 mcg Copegus 800mg vs. peginterferon alfa-2a 180µg: Odds Ratio ( 95% CI) = 2.89 (1.93 to 4.32),...P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

\* Interferon alfa-2a 3MIU Copegus 800mg vs. peginterferon alfa-2a 180mcg: Odds Ratio ( 95% CI) = 0.53 (0.33 to 0.85), ...P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084.

**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 favourable 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 favoured the combination therapy. Supportive favourable 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.

## 5.2 Pharmacokinetic properties

Ribavirin is absorbed rapidly following oral administration of a single dose of Copegus (median  $T_{max}$  = 1-2 hours). The mean terminal phase half-life of ribavirin following single doses of Copegus range from 140 to 160 hours. Ribavirin data from the literature demonstrates absorption is extensive with approximately 10% of a radiolabeled dose excreted in the faeces. 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<sub>0-t</sub> following single doses of 200-1,200 milligrams ribavirin. Mean apparent oral clearance of ribavirin following single 600 milligram doses of Copegus ranges from 22 to 29 litres/hour. Volume of distribution is approximately 4,500 litres following administration of Copegus. Ribavirin does not bind to plasma proteins.

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following single oral doses 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 es-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.

Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway, 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid 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<sub>12hr</sub> based on literature data. Following oral dosing with 600 milligrams BID, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations of approximately 2,200 ng/ml. Upon discontinuation of dosing the half-life was approximately 300 hours, which probably reflects slow elimination from non-plasma compartments.

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

**Renal function:** Single-dose ribavirin pharmacokinetics were altered (increased AUC<sub>0-t</sub> and  $C_{max}$ ) in patients with renal dysfunction compared with control subjects whose creatinine clearance was greater than 90 ml/minute. The clearance of ribavirin is substantially reduced in patients with serum creatinine  $> 2$  mg/dl or creatinine clearance  $< 50$  ml/min. There are insufficient data on the safety and efficacy of ribavirin in such patients to support recommendations for dose adjustments. Plasma concentrations of ribavirin are essentially unchanged by haemodialysis.

**Hepatic function:** Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C) are similar to those of normal controls.

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

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

Population Pharmacokinetics: A population pharmacokinetic analysis was performed using plasma concentration values from five clinical trials. While body weight and race were statistically significant covariates in the clearance model only the effect of body weight was clinically significant. Clearance increased as a function of body weight and was predicted to vary from 17.7 to 24.8 L/h over a weight range of 44 to 155 kg. Creatinine clearance (as low as 34 ml/min) did not affect ribavirin clearance.

### 5.3 Preclinical safety data

Ribavirin is embryotoxic and/or teratogenic at doses well below the recommended human dose in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the dose. Survival of foetuses and offspring is reduced.

Erythrocytes are a primary target of toxicity for ribavirin in animal studies, including studies in dogs and monkeys. Anaemia occurs shortly after initiation of dosing, but is rapidly reversible upon cessation of treatment. Hypoplastic anaemia was observed only in rats at the high dose of 160 milligrams/kg/day in the subchronic study.

Reduced leucocyte and/or lymphocyte counts were consistently noted in the repeat-dose rodent and dog toxicity studies with ribavirin and transiently in monkeys administered ribavirin in the subchronic study. Repeat-dose rat toxicity studies showed thymic lymphoid depletion and/or depletion of thymus-dependent areas of the spleen (periarteriolar lymphoid sheaths, white pulp) and mesenteric lymph node. Following repeat-dosing of dogs with ribavirin, increased dilatation/necrosis of the intestinal crypts of the duodenum was noted, as well as chronic inflammation of the small intestine and erosion of the ileum.

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 in vivo mouse micronucleus assays. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. Ribavirin is a possible human carcinogen.

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 anaemia, the severity of which was greater than that produced by either active substance alone.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core:*

Pregelatinised maize starch  
Sodium starch glycolate (Type A)  
Microcrystalline cellulose  
Maize starch  
Magnesium stearate



*Film-coating:*

Hypromellose

Talc

Titanium dioxide (E171)

Yellow iron oxide (E172)

Red iron oxide (E172)

Ethylcellulose aqueous dispersion

Triacetin

## **6.2 Incompatibilities**

Not applicable

## **6.3 Shelf life**

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

Copegus is supplied in high density polyethylene (HDPE) bottles with a child-resistant polypropylene screw cap containing 168 tablets.

## **6.6 Special precautions for disposal**

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

## **7 PARALLEL PRODUCT AUTHORISATION HOLDER**

PCO Manufacturing

Unit 10, Ashbourne Business Park

Rath

Ashbourne

Co. Meath

## **8 PARALLEL PRODUCT AUTHORISATION NUMBER**

PPA 465/194/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 6th July 2007

Date of last renewal: 6th July 2012

**10 DATE OF REVISION OF THE TEXT**

February 2013