Copegus®

Ribavirin

FILM-COATED TABLETS 200 mg

1. NAME OF THE MEDICINAL PRODUCT

Copegus 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of ribavirin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Copegus in combination with peginterferon alfa-2a or interferon alfa-2a is indicated in adult patients, 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).
Copegus, in combination with peginterferon alfa-2a, is indicated in naive patients and patients who have failed previous treatment with interferon alpha (pegylated or non-pegylated) alone or in combination therapy with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated, and monitored, by a physician experienced in the management of chronic hepatitis C.
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 prescribing information of peginterferon alfa-2a or interferon alfa-2a for prescribing information particular to either of these products.

Method of Administration

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

Posology

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

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

Posology in combination with peginterferon alfa-2a:

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

Duration of treatment
The duration of combination therapy with peginterferon alfa-2a depends on viral genotype. Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 regardless of pre-treatment viral load should receive 48 weeks of therapy.
Treatment for 24 weeks may be considered in patients infected with
- genotype 1 with low viral load (LVL) (≤800,000 IU/ml) at baseline or
- genotype 4

who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1). In these patients, tolerability to combination therapy and additional prognostic factors such as degree of fibrosis should be taken into account when deciding on treatment duration. Shortening the treatment duration in patients with genotype 1 and high viral load (HVL) (>800, 000 IU/ml) at baseline who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24 should be considered with even more caution since the limited data available suggest that this may significantly negatively impact the sustained virologic response.

Patients infected with HCV genotype 2 or 3 who have detectable HCV RNA at week 4, regardless of pre-treatment viral load should receive 24 weeks of therapy. Treatment for only 16 weeks may be considered in selected patients infected with genotype 2 or 3 with LVL (≤800,000 IU/ml) at baseline who become HCV negative by week 4 of treatment and remain HCV negative by week 16. Overall 16 weeks of treatment may be associated with a lower chance of response and is associated with a higher risk of relapse than a 24 week treatment duration (see section 5.1). In these patients, tolerability to combination therapy and the presence of additional clinical or prognostic factors such as degree of fibrosis should be taken into account when considering deviations from standard 24 weeks treatment duration. Shortening the treatment duration in patients infected with genotype 2 or 3 with HVL (>800,000 IU/ml) at baseline who become HCV negative by week 4 should be considered with more caution as this may significantly negatively impact the sustained virological response (see Table 1).

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

Table 1 Copegus Dosing Recommendations in Combination with Peginterferon alfa-2a for HCV patients			
Genotype	**Daily Copegus Dose**	**Duration of treatment**	**Number of 200 mg tablets**
Genotype 1 LVL with RVR*	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks	5 (2 morning, 3 evening) 6 (3 morning, 3 evening)
Genotype 1 HVL with RVR*	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks	5 (2 morning, 3 evening) 6 (3 morning, 3 evening)
Genotype 4 with RVR*	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks	5 (2 morning, 3 evening) 6 (3 morning, 3 evening)
Genotype 1 or 4 without RVR*	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks	5 (2 morning, 3 evening) 6 (3 morning, 3 evening)
Genotype 2 or 3 LVL with RVR**	800 mg[(a)]	16 weeks[(a)] or 24 weeks	4 (2 morning, 2 evening)
Genotype 2 or 3 HVL with RVR**	800 mg	24 weeks	4 (2 morning, 2 evening)
Genotype 2 or 3 without RVR**	800 mg	24 weeks	4 (2 morning, 2 evening)

*RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24;
**RVR = rapid viral response (HCV RNA negative) by week 4
LVL= ≤800,000 IU/ml; HVL= >800,000 IU/ml
[(a)] It is presently not clear whether a higher dose of Copegus (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

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

Chronic hepatitis C – Prior Treatment Non-responder and Relapser Patients:
The recommended dosage of Pegasys and COPEGUS combination therapy is PEGASYS 180 µg once a week by subcutaneous administration in the abdomen or thighFor patients < 75 kg and ≥ 75 kg, 1000 mg and 1200 mg of COPEGUS respectively, should be administered daily.
COPEGUS should be administered in divided doses (morning and evening) with food.
Patients who have detectable virus at week 12 should stop therapy.
The recommended duration of therapy is up to 72 weeks in genotype 1 or 4 patients and 48 weeks in genotype 2 or 3 patients.

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 is currently being studied.
A duration of therapy less than 48 weeks has not been adequately studied.

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

Table 2	**Predictive Value of Week 12 Virological Response at the Recommended Dosing Regimen while receiving Copegus and peginterferon Combination Therapy**					
Genotype	**Negative**			**Positive**		
	No response by week 12	No sustained response	Predictive Value	Response by week 12	Sustained response	Predictive Value
Genotype 1 (N= 569)	102	97	**95%** (97/102)	467	271	**58%** (271/467)
Genotype 2 and 3 (N=96)	3	3	**100%** (3/3)	93	81	**87%** (81/93)

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

Predictability of response and non-response – treatment-experienced patients
In non-responder patients re-treated for 48 or 72 weeks, viral suppression at week 12 (undetectable HCV RNA defined as <50 IU/ml) has been shown to be predictive for sustained virological response. The probabilities of not achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was not achieved at week 12 were 96% (363 of 380) and 96% (324 of 339), respectively. The probabilities of achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was achieved at week 12 were 35% (20 of 57) and 57% (57 of 100), respectively.

Posology in combination with interferon alfa-2a:

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

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

Table 3	**Copegus Dosing Recommendations in Combination with Interferon alfa-2a**		
Patient weight (kg)	**Daily Copegus dose**	**Duration of treatment**	**Number of 200 mg tablets**
<75	1,000 mg	24 or 48 weeks	5 (2 morning, 3 evening)
≥75	1,200 mg	24 or 48 weeks	6 (3 morning, 3 evening)

Dosage modification for adverse reactions
Please refer to the prescribing information 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 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.

Dose modification of Copegus depends on medicinal products that it is being combined with.
If a patient has a severe adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 4 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

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 cut-off of 75 kg) of ribavirin give rise to substantial increases in plasma concentrations of ribavirin in patients with renal impairment. The total daily dose of Copegus should be reduced for patients with creatinine clearance less than or equal to 50 ml/min as shown in Table 5 *(see also section 5.2).*

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 (see section 4.4).

If severe adverse reactions or laboratory abnormalities develop, Copegus should be discontinued, if appropriate, until the adverse reactions abate or decrease in severity. If intolerance persists after restarting Copegus, Copegus therapy should be discontinued. No data are available for pediatric subjects with renal impairment.

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

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

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

A case by case benefit/risk assessment with respect to the use of Copegus in children is needed (see section 4.4).

4.3 Contraindications

See peginterferon alfa-2a or interferon alfa-2a prescribing information for contraindications related to either of these products.
Copegus is contraindicated in the following:
- hypersensitivity to ribavirin or to any of the excipients listed in section 6.1.
- pregnant women (see section 4.4). Copegus must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
- women who are breast-feeding (see section 4.6).
- a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months.
- haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia).

4.4 Special warnings and precautions for use

Copegus monotherapy must not be used.

Combination therapy of Copegus with (peg)interferon alfa.
There are several severe adverse reactions associated with the combination therapy of ribavirin with (peg) interferon alfa. These include:

- Severe psychiatric and central nervous system effects (such as depression, suicidal ideation, attempted suicide and aggressive behavior, etc.)
- Severe ocular disorders
- Dental and periodontal disorders
- Growth inhibition in children and adolescents that may be irreversible in some patients

Please refer to the Product Information of (peg) interferon alfa for details on the recommendations of monitoring and management regarding these adverse reactions before initiating therapy.

Teratogenic risk: See section 4.6.
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 continuous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during treatment with ribavirin. For laboratory monitoring of pregnancy please refer to Laboratory tests.

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

Haemolysis and Cardiovascular system: A decrease in haemoglobin levels to <10 g/dl was observed in up to 15% of patients treated for 48 weeks with Copegus 1000/1200 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. 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 the start of therapy and monitored clinically during therapy; if any deterioration occurs, stop therapy (see section 4.2). Patients with a history of congestive heart failure, myocardial infarction, and/or previous or current arrhythmic disorders must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy.

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

myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see section 4.5).

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

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

Liver function: In patients who develop evidence of hepatic decompensation during treatment, Copegus in combination with peginterferon alfa-2a or interferon alfa-2a should be discontinued. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued.

Renal impairment: The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of Copegus, preferably by estimating the patient's creatinine clearance. Substantial increases in ribavirin plasma concentrations are seen in patients with serum creatinine >2 mg/dl or with creatinine clearance <50 ml/minute, therefore Copegus dose adjustments are recommended in these patients (see sections 4.2 and 5.2).
Haemoglobin concentrations should be monitored intensively during treatment and corrective action taken as necessary (see section 4.2).

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

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

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

Co-infected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with Copegus in combination with interferons. Baseline variables in co-infected cirrhotic patients that may be associated with hepatic decompensation include: increased serum bilirubin, decreased haemoglobin, increased alkaline phosphatase or decreased platelet count, and treatment with didanosine (ddI). Caution should therefore be exercised when adding peginterferon alfa-2a and Copegus to HAART (see section 4.5).
The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).
During treatment co-infected patients should be closely monitored for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function; e.g., Child-Pugh score of 7 or greater). The Child-Pugh scoring may be affected by factors related to treatment (i.e. indirect hyperbilirubinemia, decreased albumin) and not necessarily attributable to hepatic decompensation. Treatment with Copegus in combination with peginterferon alfa-2a or interferon alfa-2a should be discontinued immediately in patients with hepatic decompensation.

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

Laboratory tests: Standard haematologic tests and blood chemistries (complete blood count [CBC] and differential, platelet count, electrolytes, glucose, serum creatinine, liver function tests, uric acid) must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of Copegus

Haemoglobin ≥12 g/dl (females); ≥13 g/dl (males)

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

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

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

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

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

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

Didanosine (ddI): Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased *in vitro* when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactataemia/lactic acidosis have been reported with use of ribavirin.

Azathioprine: Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of Copegus and peginterferon alfa-2a concomitantly with azathioprine should be avoided. In individual cases where the benefit of administering Copegus concomitantly with azathioprine warrants the potential risk, it is recommended that close haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped (see section 4.4).

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

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

4.6 Fertility, pregnancy and lactation

Preclinical data: Significant teratogenic and/or embryocidal potential have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses well below the recommended human dose. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the ribavirin dose. Survival of foetuses and offspring was reduced.

Female patients: Copegus must not be used by women who are pregnant (see section 4.3 and section 4.4). Extreme care must be taken to avoid pregnancy in female patients. Copegus therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential must use a form of effective contraception, during treatment and for 4 months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within 4 months from stopping treatment the patient must be advised of the significant teratogenic risk of ribavirin to the foetus.

Male patients and their female partners: Extreme care must be taken to avoid pregnancy in partners of male patients taking Copegus. Ribavirin accumulates intracellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Either male patients or their female partners of childbearing age must, therefore, be counselled to use a form of effective contraception during treatment with Copegus and for 7 months after treatment has been concluded. A pregnancy test must be performed before therapy is started. Men whose partners are pregnant must be instructed to use a condom to minimise delivery of ribavirin to the partner.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The salient safety issue of ribavirin is hemolytic anemia occurring within the first weeks of therapy. The hemolytic anemia associated with ribavirin therapy may result in deterioration of cardiac function and/or worsening of preexisting cardiac disease. An increase in uric acid and indirect bilirubin values associated with haemolysis were also observed in some patients (see below and section 4.4).

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

The adverse events listed in this section are reported in clinical trials and/or as adverse drug reactions from spontaneous reports primarily when Copegus was used in combination with interferon alfa-2a or peginterferon alfa-2a.

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

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

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

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

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

Chronic hepatitis C and Human Immunodeficiency Virus Co-infection
In HIV-HCV co-infected patients, the clinical adverse event profiles reported for peginterferon alfa-2a, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients. For HIV-HCV patients receiving Copegus and peginterferon alfa-2a combination therapy other undesirable effects have been reported in ≥1% to ≤ 2% of patients: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia. Peginterferon alfa-2a treatment was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of peginterferon alfa-2a had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited

safety data are available in co-infected patients with CD4+ cell counts <200/µl (see peginterferon alfa-2a prescribing information).

Table 6 shows the undesirable effects reported in patients who have received Copegus primarily in combination with peginterferon alfa-2a or interferon alfa-2a.

Table 4 Undesirable Effects Reported with Copegus primarily in combination with Peginterferon alfa-2a or Interferon alfa-2a for HCV Patients

Body system	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Very rare <1/10,000	Frequency not known*
Infections and infestations		Upper respiratory infection, bronchitis, oral candidiasis, herpes simplex	Lower respiratory tract infection, pneumonia, urinary tract infection, skin infection	Endocarditis, Otitis externa		
Blood and lymphatic system disorders	Anaemia, neutropenia	Thrombo-cytopenia, lymphadeno-pathy		Pancytopenia	Aplastic anaemia	Pure red cell aplasia
Immune system disorders			Sarcoidosis, thyroiditis	Anaphylaxis, systemic lupus erythemato-sus, rheumatoid arthritis	idiopathic or thrombotic thrombocyto-penic purpura	Liver and renal graft rejection, Vogt-Koyanagi-Harada disease
Endocrine disorders		Hypo-thyroidism, hyper-thyroidism	Diabetes			
Metabolism and Nutrition Disorders	Anorexia		Dehydration			
Psychiatric disorders	Depression, insomnia	Mood alteration, emotional disorders, anxiety, aggression, nervousness, libido decreased	Suicidal ideation, hallucina-tions, anger	Suicide, psychotic disorder		Mania, bipolar disorders, homicidal ideation
Nervous system disorders	Headache, dizziness, concentration impaired	Memory impairment, syncope, weakness, migraine, hypoaesthe-sia, hyperaesthe-sia, paraesthesia, tremor, taste disturbance, nightmares, somnolence	Peripheral neuropathy	Coma, convulsions, facial palsy	Cerebral ischaemia	

Body system	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10,000 to <1/1000**	**Very rare <1/10,000**	**Frequency not known***
Eye disorders		Vision blurred, eye pain, eye inflammation, xerophthalmia	Retinal haemorrhage	Optic neuropathy, papilloedema, retinal vascular disorder, retinopathy, corneal ulcer	Vision loss	Serous retinal detachment
Ear and labyrinth disorders		Vertigo, earache, tinnitus	Hearing loss			
Cardiac disorders		Tachycardia, palpitations, oedema peripheral		Myocardial infarction, congestive heart failure, angina, supraventri-cular tachycardia arrhythmia, atrial fibrillation, pericarditis		
Vascular disorders		Flushing, hypotension	Hypertension	Cerebral haemorrhage, vasculitis		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough	Dyspnoea exertional, epistaxis, nasopharyn-gitis, sinus congestion, nasal congestion, rhinitis, sore throat	Wheezing	Interstitial pneumonitis with fatal outcome, pulmonary embolism		
Gastrointestinal disorders	Diarrhoea, nausea, abdominal pain	Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, constipation, dry mouth	Gastrointes-tinal bleeding, cheilitis, gingivitis	Peptic ulcer, pancreatitis		Colitis ischaemic, colitis ulcerative, tongue pigmentation
Hepato-biliary disorders			Hepatic dysfunction	Hepatic failure, cholangitis, fatty liver		

Body system	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	Very rare <1/10,000	Frequency not known*
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, pruritus, dry skin	Rash, sweating increased, psoriasis, urticaria, eczema, skin disorder, photosensiti-vity reaction, night sweats			Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskelet al pain, muscle cramps		Myositis		Rhabdomyo-lysis
Renal and Urinary Disorders						Renal failure, nephrotic syndrome
Reproductive system and breast disorders		Impotence				
General disorders and administration site conditions	Pyrexia, rigors, pain, asthenia, fatigue, irritability	Chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst				
Investigations		Weight decreased				
Injury and poisoning				Substance overdose		

* Identified in postmarketing experience

Laboratory values: In clinical trials of Copegus in combination with peginterferon alfa-2a or interferon alfa-2a, the majority of cases of abnormal laboratory values were managed with dose modifications (see section 4.2). With peginterferon alfa-2a and Copegus combination treatment, up to 2% of patients experienced increased ALT levels that led to dose modification or discontinuation of treatment.

Haemolysis is the dose limiting toxicity of ribavirin therapy. A decrease in haemoglobin levels to <10 g/dl was observed in up to 15% of patients treated for 48 weeks with Copegus 1000/1200 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. In most cases the decrease in haemoglobin occurred early in the treatment period and stabilised concurrently with a compensatory increase in reticulocytes.

Most cases of anaemia, leucopenia and thrombocytopenia were mild (WHO grade 1). WHO grade 2 laboratory changes were reported for haemoglobin (4% of patients), leucocytes (24% of patients) and thrombocytes (2% of patients). Moderate (absolute neutrophil count (ANC): 0.749-0.5x10^9/l) and severe (ANC: <0.5x10^9/l) neutropenia was observed in 24% (216/887) and 5% (41/887) of patients receiving 48 weeks of Copegus 1000/1200 mg 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^3 was observed in 13% and 11% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm^3 was observed in 10% and 8% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Anaemia (haemoglobin <10 g/dl) was reported in 7% and 14% of patients treated with peginterferon alfa-2a monotherapy or in combination therapy, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the following links: http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic%40moh.health.gov.il or mail to: ADR@MOH.health.gov.il.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 µg 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 efficacy and safety

Copegus in combination with peginterferon alfa-2a

Predictability of response
Please refer to the peginterferon alfa-2a Prescribing Information

Study results in treatment-naive patients
Efficacy and safety of the combination of Copegus and peginterferon alfa-2a were established in two pivotal studies (NV15801 + NV15942), including a total of 2405 patients. The study population comprised interferon-naive 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 15). 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 µg 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 9, 11 and 15 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 7 Virological Response in the overall population (including non-cirrhotic and cirrhotic patients)

	Study NV15942	**Study NV15801**	
	Copegus 1,000/1,200 mg & Peginterferon alfa-2a 180 µg (N=436) 48 weeks	Copegus 1,000/1,200 mg & Peginterferon alfa-2a 180 µg (N=453) 48 weeks	Ribavirin 1,000/1,200 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

The virological responses of HCV monoinfected patients treated with Copegus and peginterferon alfa-2a combination therapy in relation to genotype and pre-treatment viral load and in relation to genotype, pre-treatment viral load and rapid virological response at week 4 are summarised in Table 8 and Table 9 respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype, baseline viral load and virological response at week 4 (see Tables 9 and 10).

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

Table 8 Sustained Virological Response based on Genotype and Pre-treatment Viral Load after Copegus Combination Therapy with peginterferon alfa-2a

	Study NV15942				**Study NV15801**	
	Copegus 800 mg & **PEG-IFN alfa-2a** 180 µg 24 weeks	**Copegus** 1000/1200 mg & **PEG-IFN alfa-2a** 180 µg 24 weeks	**Copegus** 800 mg & **PEG-IFN alfa-2a** 180 µg 48 weeks	**Copegus** 1000/1200 mg & **PEG-IFN alfa-2a** 180 µg 48 weeks	**Copegus** 1000/1200 mg & **PEG-IFN alfa-2a** 180 µg 48 weeks	**Ribavirin** 1000/1200 mg & **Interferon 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)

Low viral load= ≤800,000 IU/ml; High viral load= >800,000 IU/ml
*Copegus 1000/1200 mg + peginterferon alfa-2a 180 µg, 48 w vs. Copegus 800 mg + peginterferon alfa-2a 180 µg, 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 µg, 48 w vs. Copegus 1000/1200 mg + peginterferon alfa-2a 180 µg, 24 w: Odds Ratio (95% CI) = 2.12 (1.30 to 3.46) P-value (stratified Cochran-Mantel-Haenszel test) = 0.002

The possibility to consider shortening treatment duration to 24 weeks in genotype 1 and 4 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response at week 4 in studies NV15942 and ML17131 (see Table 9).

Table 9 Sustained Virological Response Based on Rapid Viral Response at week 4 for Genotype 1 and 4 after Copegus Combination Therapy with Peginterferon alfa-2a in HCV Patients

	Study NV15942		Study ML17131
	Copegus 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 24 weeks	**Copegus** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 48 weeks	**Copegus** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 24 weeks
Genotype 1 RVR	90% (28/31)	92% (47/51)	77% (59/77)
Low viral load	93% (25/27)	96% (26/27)	80% (52/65)
High viral load	75% (3/4)	88% (21/24)	58% (7/12)
Genotype 1 non RVR	24% (21/87)	43% (95/220)	-
Low viral load	27% (12/44)	50% (31/62)	-
High viral load	21% (9/43)	41% (64/158)	-
Genotype 4 RVR	(5/6)	(5/5)	92% (22/24)
Genotype 4 non RVR	(3/6)	(4/6)	-

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

Although limited, data indicated that shortening treatment to 24 weeks might be associated with a higher risk of relapse (see Table 10).

Table 10 Relapse of Virological Response at the End of Treatment for Rapid Virological Response Population

	Study NV15942		Study NV15801
	Copegus 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 24 weeks	**Copegus** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 48 weeks	**Copegus** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 48 weeks
Genotype 1 RVR	6.7% (2/30)	4.3% (2/47)	0% (0/24)
Low viral load	3.8% (1/26)	0% (0/25)	0% (0/17)
High viral load	25% (1/4)	9.1% (2/22)	0% (0/7)
Genotype 4 RVR	(0/5)	(0/5)	0% (0/4)

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on the sustained rapid virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 11).

In study NV17317 in patients infected with viral genotype 2 or 3, all patients received peginterferon alfa-2a 180 µg sc qw and a Copegus dose of 800 mg and were randomised to treatment for either 16 or 24 weeks. Overall treatment for 16 weeks resulted in lower sustained viral response (65%) than treatment for 24 weeks (76%) ($p < 0.0001$).

The sustained viral response achieved with 16 weeks of treatment and with 24 weeks of treatment was also examined in a retrospective subgroup analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline (see Table 11).

Table 11 Sustained Virological Response Overall and Based on Rapid Viral Response by Week 4 for Genotype 2 or 3 after Copegus Combination Therapy with Peginterferon alfa-2a in HCV Patients

	Study NV17317			
	Copegus 800 mg & **Peginterferon alfa-2a** 180 µg 16 weeks	**Copegus** 800 mg & **Peginterferon alfa-2a** 180 µg 24 weeks	**Treatment difference** **$_{95\%}$CI**	**p value**
Genotype 2 or 3	65% (443/679)	76% (478/630)	-10.6% [-15.5% ; -0.06%]	P<0.0001
Genotype 2 or 3 RVR	82% (378/461)	90% (370/410)	-8.2% [-12.8% ; -3.7%]	P=0.0006
Low viral load	89% (147/166)	94% (141/150)	-5.4% [-12% ; 0.9%]	P=0.11
High viral load	78% (231/295)	88% (229/260)	-9.7% [-15.9% ; -3.6%]	P=0.002

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

It is presently not clear whether a higher dose of Copegus (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The data indicated that shortening treatment to 16 weeks is associated with a higher risk of relapse (see Table 12)

Table 12 Relapse of Virological Response after the End of Treatment in Genotype 2 or 3 Patients with a Rapid Viral Response

	Study NV17317			
	Copegus 800 mg & **Peginterferon alfa-2a** 180 µg 16 weeks	**Copegus** 800 mg & **Peginterferon alfa-2a** 180 µg 24 weeks	**Treatment difference** **$_{95\%}$CI**	**p value**
Genotype 2 or 3 RVR	15% (67/439)	6% (23/386)	9.3% [5.2% ; 13.6%]	P<0.0001
Low viral load	6% (10/155)	1% (2/141)	5% [0.6% ; 10.3%]	P=0.04
High viral load	20% (57/284)	9% (21/245)	11.5% [5.6% ; 17.4%]	P=0.0002

Chronic hepatitis C prior treatment non-responder patients

In study MV17150, patients who were non-responders to previous therapy with pegylated interferon alfa-2b plus ribavirin were randomised to four different treatments:
- peginterferon alfa-2a 360 µg/week for 12 weeks, followed by 180 µg/week for a further 60 weeks
- peginterferon alfa-2a 360 µg/week for 12 weeks, followed by 180 µg/week for a further 36 weeks
- peginterferon alfa-2a 180 µg/week for 72 weeks
- peginterferon alfa-2a 180 µg/week for 48 weeks

All patients received Copegus (1000 or 1200 mg/day) in combination with peginterferon alfa-2a. All treatment arms had 24 week treatment-free follow-up.

Multiple regression and pooled group analyses evaluating the influence of treatment duration and use of induction dosing clearly identified treatment duration for 72 weeks as the primary driver for achieving a sustained virological response. Differences in sustained virological response (SVR) based on treatment duration, demographics and best responses to previous treatment are displayed in Table 13.

Table 13 Week 12 Virological Response (VR) and Sustained Virological Response (SVR) in Patients with Virological Response at Week 12 after Treatment with Copegus and Peginterferon alfa-2a Combination Therapy in Non-Responders to Peginterferon alfa-2b plus Ribavirin

	Copegus 1000/1200 mg & **Peginterferon alfa-2a** 360/180 or 180 µg 72 or 48 Weeks (N = 942) **Pts with VR at Wk 12 [a] (N = 876)**	**Copegus** 1000/1200 mg & **Peginterferon alfa-2a** 360/180 or 180 µg 72 Weeks (N = 473) **SVR in Pts with VR at Wk 12 [b] (N = 100)**	**Copegus** 1000/1200 mg & **Peginterferon alfa-2a** 360/180 or 180 µg 48 Weeks (N = 469) **SVR in Pts with VR at Wk 12 [b] (N = 57)**
Overall	18% (157/876)	57% (57/100)	35% (20/57)
Low viral load	35% (56/159)	63% (22/35)	38% (8/21)
High viral load	14% (97/686)	54% (34/63)	32% (11/34)
Genotype 1/4	17% (140/846)	55% (52/94)	35% (16/46)
Low viral load	35% (54/154)	63% (22/35)	37% (7/19)
High viral load	13% (84/663)	52% (30/58)	35% (9/26)
Genotype 2/3	58% (15/26)	(4/5)	(3/10)
Low viral load	(2/5)	—	(1/2)
High viral load	(11/19)	(3/4)	(1/7)
Cirrhosis Status			
Cirrhosis	8% (19/239)	(6/13)	(3/6)
Noncirrhosis	22% (137/633)	59% (51/87)	34% (17/50)
Best Response during Previous Treatment			
≥2log$_{10}$ decline in HCV RNA	28% (34/121)	68% (15/22)	(6/12)
<2log$_{10}$ decline in HCV RNA	12% (39/323)	64% (16/25)	(5/14)
Missing best previous response	19% (84/432)	49% (26/53)	29% (9/31)

High viral load = >800,000 IU/ml, low viral load = ≤800,000 IU/ml.
a Patients who achieved viral suppression (undetectable HCV RNA, <50 IU/ml) at week 12 were considered to have a virological response at week 12. Patients missing HCV RNA results at week 12 have been excluded from the analysis.
b Patients who achieved viral suppression at week 12 but were missing HCV RNA results at the end of follow-up were considered to be non-responders

In the HALT-C study, patients with chronic hepatitis C and advanced fibrosis or cirrhosis who were non-responders to previous treatment with interferon alfa or pegylated interferon alfa, monotherapy or in combination therapy with ribavirin, were treated with peginterferon alfa-2a 180 µg/week and Copegus 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on peginterferon alfa-2a plus Copegus combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. The probability for sustained virological response varied depending upon the previous treatment regimen (see Table 14).

Table 14 Sustained Virological Response in HALT-C by Previous Treatment Regimen in Non-Responder Population	
Previous Treatment	**Copegus** 1000/1200 mg & **Peginterferon alfa-2a** 180 µg 48 weeks
Interferon	27% (70/255)
Pegylated interferon	34% (13/38)
Interferon plus ribavirin	13% (90/692)
Pegylated interferon plus ribavirin	11% (7/61)

HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomised to receive peginterferon alfa-2a 180 µg/week with a Copegus dose of 800 mg/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.

Children and adolescents
In the investigator sponsored CHIPS study (Chronic Hepatitis C International Paediatric Study), 65 children and adolescents (6-18 years) with chronic HCV infection were treated with peginterferon alfa-2a 100 µg/m^2 sc once weekly and Copegus 15 mg/kg/day, for 24 weeks (genotypes 2 and 3) or 48 weeks (all other genotypes). Preliminary and limited safety data demonstrated no obvious departure from the known safety profile of the combination in adults with chronic HCV infection, but, importantly, the potential impact on growth has not been reported. Efficacy results were similar to those reported in adults.

HIV-HCV co-infected patients
The virological responses of patients treated with Copegus and peginterferon alfa-2a combination therapy in relation to genotype and pre-treatment viral load for HIV-HCV co-infected patients are summarised below in Table 15.

Table 15 Sustained Virological Response based on Genotype and Pre-treatment Viral Load after Copegus Combination Therapy with peginterferon alfa-2a in HIV-HCV co-infected patients			
	Study NR15961		
	Interferon alfa-2a 3 MIU & **Copegus 800 mg** 48 weeks	**Peginterferon alfa-2a** 180 µg & **Placebo** 48 weeks	**Peginterferon alfa-2a** 180 µg & **Copegus 800 mg** 48 weeks
All patients	12% (33/285)*	20% (58/286)*	40% (116/289)*
Genotype 1 Low viral load High viral load	7% (12/171) 19% (8/42) 3% (4/129)	14% (24/175) 38% (17/45) 5% (7/130)	29% (51/176) 61% (28/46) 18% (23/130)
Genotype 2-3 Low viral load High viral load	20% (18/89) 27% (8/30) 17% (10/59)	36% (32/90) 38% (9/24) 35% (23/66)	62% (59/95) 61% (17/28) 63% (42/67)

Low viral load= ≤800,000 IU/ml; High viral load= >800,000 IU/ml
* peginterferon alfa-2a 180 µg + Copegus 800 mg vs. Interferon alfa-2a 3 MIU + Copegus 800 mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), P-value (stratified Cochran-Mantel-Haenszel test) = <0.0001; peginterferon alfa-2a 180 µg + Copegus 800 mg vs. peginterferon alfa-2a 180 µg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), P-value (stratified Cochran-Mantel-Haenszel test) = <0.0001; Interferon alfa-2a 3 MIU + Copegus 800 mg vs. peginterferon alfa-2a 180 µg: Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), P-value (stratified Cochran-Mantel-Haenszel test) = <0.0084

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared treatment using peginterferon alfa-2a 180 µg/week and either Copegus 800 mg or 1000 mg (<75 kg)/1200 mg (≥75 kg) daily for 48 weeks. The study was not powered for efficacy considerations. The safety profiles in both Copegus groups were consistent with the known safety profile of peginterferon alfa-2a plus Copegus combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose Copegus arm.

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 naive (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 naive 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 radiolabelled dose excreted in the faeces. However, absolute bioavailability is approximately 45%-65%, which appears to be due to first pass metabolism. There is an approximately linear relationship between dose and AUC_{tf} following single doses of 200-1,200 mg ribavirin. Mean apparent oral clearance of ribavirin following single 600 mg doses of Copegus ranges from 22 to 29 litres/hour. Volume of distribution is approximately 4,500 1itres 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 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.

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 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 $AUC_{(0\text{-}192h)}$ 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 and interferon alfa-2b and ribavirin. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food.

Renal function: The apparent clearance of ribavirin is reduced in patients with creatinine clearance ≤50 ml/min, including patients with ESRD on chronic haemodialysis, exhibiting approximately 30% of the value found in patients with normal renal function. Based on a small study in patients with moderate or severe renal impairment (creatinine clearance ≤50 ml/min) receiving reduced daily doses of 600 mg and 400 mg of Copegus, respectively ribavirin plasma exposure (AUC) was found to be 20 to 30% higher compared to patients with normal renal function (creatinine clearance >80 ml/min) receiving the standard Copegus dose. In patients with ESRD on chronic haemodialysis and who received 200 mg daily doses of Copegus, mean ribavirin exposure (AUC) was found to be approximately 20% lower compared to patients with normal renal function receiving the standard 1000/1200 mg Copegus daily dose. Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%; however, due to the large volume of distribution of ribavirin, significant amounts of ribavirin are not effectively removed from the body by haemodialysis. Increased rates of adverse drug reactions were observed in patients with moderate and severe renal impairment receiving the doses evaluated in this study.

Based on pharmacokinetic modelling and simulation, dose adjustments are recommended in patients with significant renal impairment (see section 4.2). These adjusted doses are expected to provide ribavirin plasma exposures comparable to those achieved in patients with normal renal function receiving the standard Copegus dose. Most of the recommended doses were derived from PK modelling and simulation and have not been studied in clinical trials.

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: Refer to the PI of interferon alfa-2a or peginterferon alfa-2a that are indicated in combination with Copegus for this population.
No Copegus pharmacokinetic analysis has been performed in patients under the age of 18 years.

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.

Transfer into seminal fluid: Seminal transfer of ribavirin has been studied. Ribavirin concentrations in seminal fluid are approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentrations of ribavirin.

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 mg/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 starch
Sodium starch glycolate (type A)
Microcrystalline cellulose
Maize starch
Magnesium stearate

Film-coating:
Hypromellose
Talc
Titanium dioxide
Yellow iron oxide
Red iron oxide
Ethylcellulose aqueous dispersion (solids)
Triacetin

6.2 Incompatibilities

Not applicable

6.3 Shelf life after first opening

Shelf life after first opening: 168 days (24 weeks).

6.4 Special precautions for storage

Do not store above 30˚C

6.5 Nature and contents of container

Copegus is supplied in high density polyethylene (HDPE) bottles with a child-resistant polypropylene screw cap containing 42, 112 or 168 tablets. Not all pack sizes may be marketed.

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. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O.B 6391, Hod Hasharon, 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

128.23.30701.11

Medicine: keep out of reach of children

Copegus® is manufactured by F. Hoffmann-La Roche Ltd., Basel, Switzerland.