NAME OF THE MEDICINAL PRODUCT

Copegus 200 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 milligrams of ribavirin.
For excipients, see **6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablet

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. 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

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

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

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

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

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

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 Anemia**, 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. thalassemia, sickle-cell anaemia).

4.4 Special warnings and special precautions for use

Please refer to the SPC of peginterferon alfa-2a or interferon alfa-2a for futher 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 maybe possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

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. 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): 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: 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; hepatic decompensation in HIV/HCV patients with cirrhosis). 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**).

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

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_{tf} decreased 14%. It is possible that the decreased bioavailability in this study was due to delayed transit of ribavirin or modified pH. This interaction is not considered to be clinically relevant.

*Nucleoside analogs***:** Ribavirin was shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these findings is unknown. However, these *in vitro* findings raise the possibility that concurrent use of Copegus with either zidovudine or stavudine might lead to increased HIV plasma 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, although intracellular ddATP was not measured.

4.6 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 counseled 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.

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

Table 5 Safety Overview of Copegus Treatment Regimens in Combination with Peginteferon alfa-2a

	Copegus 800 mg 24 weeks & PEG-IFN alfa-2a 180 mcg	**Copegus** 1000/1200 mg 48 weeks & PEG-IFN alfa-2a 180 mcg
Serious adverse events	3%	11%
Anemia (haemoglobin < 10g/dl)	3%	15%
Ribavirin dose modification	19%	39%
Premature withdrawals due to adverse events	4%	10%
Premature withdrawals due to laboratory abnormalities	1%	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)		
	Copegus 800 mg & Peginterferon alfa-2a 180 micrograms (NV15942) 24 weeks N=207	Copegus 1,000 or1,200 mg & Peginterferon alfa-2a 180 micrograms (NV15801 + NV15942) 48 weeks N=887
Body System	%	%
Metabolism & Nutrition disorders		
Anorexia	20%	27%
Psychiatric Disorders		
Insomnia	30%	32%
Irritability	28%	24%
Depression	17%	21%
Concentration Impairment	8%	10%
Nervous system disorders		
Headache	48%	47%
Dizziness	13%	15%
Respiratory, thoracic and mediastinal disorders		
Dyspnea	11%	13%
Cough	8%	13%
Gastrointestinal Disorders		
Nausea	29%	28%
Diarrhea	15%	14%
Abdominal Pain	9%	10%
Skin and subcutaneous tissue disorders		
Alopecia	25%	24%
Pruritus	25%	21%
Dermatitis	15%	16%
Dry skin	13%	12%

TABLE 6: Adverse Reactions (≥10% Incidence in Any Treatment Group)		
	Copegus 800 mg & Peginterferon alfa-2a 180 micrograms (NV15942) 24 weeks N=207	Copegus 1,000 or1,200 mg & Peginterferon alfa-2a 180 micrograms (NV15801 + NV15942) 48 weeks N=887
Musculoskeletal, connective tissue and bone disorders		
Myalgia	42%	38%
Arthralgia	20%	22%
General disorders and administration site conditions		
Fatigue	45%	49%
Pyrexia	37%	39%
Rigors	30%	25%
Asthenia	18%	15%
Pain	9%	10%
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 on Copegus in combination with peginterferon alfa-2a			
Body system	**Common <10% - 5%**	**Common <5% -1%**	**Uncommon to Rare serious adverse events <1% - <0.1%**
Infections and infestations		herpes simplex, URI infection, bronchitis, oral candidiasis	Skin infection, lower respiratory tract infection, otitis externa, endocarditis
Neoplasms benign and malignant			Hepatic neoplasm
Blood and lymphatic system disorders		Anaemia, lymphadenopathy, thrombocytopenia	
Immune system disorders			ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE
Endocrine disorders		Hypothyroidism, hyperthyroidism	
Metabolism and nutrition disorders	Weight decrease		
Psychiatric disorders	mood alteration, emotional disorders, anxiety	Nervousness, libido decreased, aggression,	Suicide, Depression

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
Ear and labyrinth disorders		vertigo, earache	
Cardiac disorders		Palpitations, oedema peripheral, tachycardia	Arrhythmia, atrial fibrillation, pericarditis
Vascular disorders		Flushing	Cerebral hemorrhage
Respiratory, thoracic and mediastinal disorders		sore throat, dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, rhinitis, nasal congestion	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 pancreactic reaction (ie, amylase/lipase increase with or without abdominal pain)
Hepato-biliary disorders			Hepatic dysfunction, fatty liver, cholangitis
Skin and subcutaneous tissue disorders	rash, sweating increased	Eczema, night sweats, psoriasis, photosensitivity reaction, urticaria, skin disorder	
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

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), leukocytes (24% of patients) and thrombocytes (2% of patients). Moderate (absolute neutrophil count (ANC): 0.749-0.5x109/L) and severe (ANC: <0.5x109/L) neutropenia was observed in 24% (216/887) and 5% (41/887) of patients receiving 48 weeks of Copegus 1000/1200 milligrams in combination with peginterferon alfa-2a.

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

4.9 Overdose

No cases of overdose of Copegus have been reported in clinical trials. 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. No HIV/HCV co-infected patients were included in these clinical trials.

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 treatment regimens, duration of therapy and study outcome see tables 8 and 9. 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 approvimately 6 months after the end of therapy.

Table 8 Virological Response in the overall population (including non-cirrhotic and cirrhotic patients)

	Study NV15942	**Study NV15801**	
	Copegus 1,000/1,200 mg & Peginterferon alfa-2a 180 micrograms (N=436) 48 weeks	Copegus 1,000/1,200 mg & Peginterferon alfa-2a 180 micrograms (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 patients treated with Copegus and peginterferon alfa-2a combination therapy in relation to genotype and viral load are summarised in table 9. 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

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

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

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

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_{tf} 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 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 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 $AUC_{(0\text{-}192h)}$ 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: Single-dose ribavirin pharmacokinetics were altered (increased AUC_{tf} 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 starch
Sodium starch glycolate
Microcrystalline cellulose
Maize starch

Magnesium stearate

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

Copegus is supplied in high density polyethylene (HDPE) bottles with a child-resistant polypropylene screw cap containing 28, 42, 112 or 168 tablets. Not all pack sizes may be marketed.

6.6 Instructions for use and handling, and disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT