

Data Sheet

Copegus[®]

Ribavirin film-coated tablets 200 mg

Direct acting antiviral

Pharmaceutical Form

A 200 mg oval shaped film-coated tablet for oral administration.

Qualitative and Quantitative Composition

Active ingredient

Each Copegus film-coated tablet contains 200 mg of ribavirin.

Excipients

Kernel: pregelatinised starch, sodium starch glycolate, microcrystalline cellulose, maize starch, magnesium stearate.

Film-coat: ethyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, talc, iron oxide yellow, iron oxide red, triacetin.

Appearance

Copegus 200 mg tablets are light pink to pink, flat, oval, film-coated tablets with RIB and 200 engraved on one side and ROCHE on the other side.

Clinical Particulars

Therapeutic Indications

Copegus is indicated, in combination with peginterferon alfa-2a or interferon alfa-2a, for the treatment of chronic hepatitis C (CHC) in adult patients and who are positive for serum HCV RNA, including patients with compensated cirrhosis.

Please refer to peginterferon alfa-2a or interferon alfa-2a prescribing information for additional information.

Dosage and Administration

Standard dosage

Copegus is used in combination with peginterferon alfa-2a (Pegasys[®]) or interferon alfa-2a (Roferon-A[®]). The exact dose and duration of treatment depend on the interferon product used.

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

In combination with peginterferon alfa-2a

The daily dose and duration of Copegus given in combination with peginterferon alfa-2a solution for injection should be individualised based on the patient’s viral genotype and body weight (see Table 1). The daily dose of Copegus is to be administered orally in two divided doses (morning and evening) with food.

Chronic hepatitis C: treatment naïve, prior treatment non-responder and relapser patients

Table 1 Copegus Dosing Recommendations in combination with peginterferon alfa-2a for HCV patients

Genotype	Daily Copegus Dose	Duration of Treatment – naïve patients	Duration of Treatment – prior treatment non-responder and relapser patients	Number of 200 mg Tablets
Genotype 1, 4*	< 75 kg = 1000 mg	48 weeks	72 weeks	5 (2 morning, 3 evening)
	≥ 75 kg = 1200 mg	48 weeks	72 weeks	6 (3 morning, 3 evening)
Genotype 2, 3	800 mg (regardless of weight)	24 weeks	48 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.

HIV-HCV co-infection

The recommended dosage of Copegus, in combination with 180 mcg of peginterferon alfa-2a is 800 mg of Copegus daily for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with Copegus doses greater than 800 mg daily or a duration of therapy less than 48 weeks has not been studied.

Predictability of response and non-response in naïve patients

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

Table 2 Predictive Value of Week 12 Virological Response at the Recommended Dosing Regimen while receiving Copegus and Peginterferon alfa-2a Combination Therapy in HCV Patients

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, 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 Copegus (100% (130/130) or 98% (83/85), respectively). Positive predictive values of 45% (50/100) 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 in prior non-responder patients

In non-responder patients treated for 72 weeks, the best on-treatment predictor of response was viral suppression at week 12 (undetectable HCV RNA, defined as HCV RNA < 50 IU/mL). The negative predictive value of viral suppression at week 12 was 96% (324/339) and the positive predictive value was 57% (57/100).

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 6 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 for HCV Patients

Patient weight (kg)	Daily Copegus Dose	Duration of Treatment	Number of 200 mg Tablets
< 75 kg	1000 mg	24 or 48 weeks	5 (2 morning, 3 evening)
≥ 75 kg	1200 mg	24 or 48 weeks	6 (3 morning, 3 evening)

Special dosage instructions

Dosage modification for adverse reactions

Please refer to peginterferon alfa-2a or interferon alfa-2a prescribing information 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. If intolerance persists after Copegus dose adjustment, discontinuation of the medicine may be necessary.

For management of treatment-emergent anaemia, the following guidelines were developed in clinical trials (see Table 4).

Table 4 Copegus Dosage Modification Guidelines for Management of Treatment-Emergent Anaemia

Laboratory Values	Reduce Copegus dose to 600 mg/day* only if:	Discontinue Copegus if**:
Haemoglobin: Patients with no cardiac disease	< 100 g/L	< 85 g/L
Haemoglobin: Patients with history of stable cardiac disease	> 20 g/L decrease in haemoglobin during any 4 week period during treatment (permanent dose reduction)	< 120 g/L after 4 weeks of dose reduction

* 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

Dosage modification for patients undergoing long term haemodialysis

In renally impaired patients undergoing long term haemodialysis, Copegus can be safely administered at a dose of 200 mg daily (see Warnings and Precautions and Pharmacokinetics in special populations).

Use in hepatic impairment

No pharmacokinetic interaction appears between ribavirin and hepatic function. Therefore, no dose adjustment of Copegus is required in patients with hepatic impairment. The use of peginterferon alfa-2a or interferon alfa-2a is contraindicated in patients with decompensated liver disease.

Use in the elderly (≥ 65 years of age)

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

Use in patients under the age of 18 years

Safety and effectiveness of ribavirin in combination with peginterferon alfa-2a or interferon alfa-2a in these patients have not been evaluated. Treatment with Copegus is not recommended for use in children and adolescents under the age of 18.

Please refer to peginterferon alfa-2a or interferon alfa-2a prescribing information for additional information.

Contraindications

Copegus is contraindicated in patients with hypersensitivity to ribavirin or to any of the excipients.

Copegus must not be used by women who are pregnant or by men whose female partners are pregnant.

Copegus is contraindicated in patients with haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia).

Peginterferon alfa-2a and Copegus combination therapy is contraindicated in patients with hepatic decompensation.

Initiation of peginterferon alfa-2a is contraindicated in HIV–HCV patients with cirrhosis and a Child-Pugh score ≥ 6 , except if only due to indirect hyperbilirubinemia caused by medicines such as atazanavir and indinavir (please refer to the peginterferon alfa-2a prescribing information for Child-Pugh assessment).

Please refer to peginterferon alfa-2a or interferon alfa-2a prescribing information for additional information.

Warnings and Precautions

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

Copegus used in combination therapy should be administered under the guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of further therapy.

Teratogenic risk

Prior to initiation of treatment with Copegus 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 Copegus (see Pregnancy).

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.

Haemolysis and cardiovascular system

If there is any deterioration of haemoglobin blood concentration, Copegus should be suspended or discontinued (see Special dosage instructions, Table 4). Although Copegus 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 significant or unstable disease. Cardiac status must be assessed before initiation of therapy and monitored clinically during therapy. If there is any deterioration of cardiovascular status, ribavirin therapy should be stopped (see Dosage and

Administration, Table 3). It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to and during the course of treatment.

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

Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of Copegus and 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 Interactions with other Medicinal Products and other Forms of Interaction).

Organ transplant recipients

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

Hepatic 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.

Renal impairment

Copegus therapy should not be initiated in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min) who are not undergoing long term haemodialysis, unless it is considered to be essential. Copegus must be administered with extreme caution. Compared to patients with normal renal function receiving the standard 1000/1200 mg Copegus daily dose, ribavirin plasma exposures are higher in patients with moderate renal impairment after receiving 600 mg daily of Copegus, and in patients with severe renal impairment receiving as little as 400 mg daily of Copegus.

In patients who develop renal impairment (and not receiving haemodialysis) during a standard treatment course of Copegus in combination with peginterferon alfa-2a, Copegus therapy should not be continued.

Copegus therapy may be initiated in patients with end-stage renal disease (ESRD) receiving chronic haemodialysis. In these patients, most of whom received haematopoietic growth factors,

Copegus can be safely administered at a dose of 200 mg daily. ESRD patients undergoing long term haemodialysis who were administered a 200 mg daily dose exhibited ribavirin plasma exposures that were approximately 20% lower compared to patients with normal renal function receiving the standard 1000/1200 mg Copegus daily dose (see Special Dosage Instructions and Pharmacokinetic Properties)

It is recommended that renal function be evaluated in all patients prior to initiation of Copegus, preferably by estimating the patient's creatinine clearance. Patients undergoing long term haemodialysis receiving Copegus should be carefully monitored.

Laboratory tests

Standard haematologic tests and blood chemistries (full blood count [FBC] and differential, platelet count, electrolytes, serum creatinine, liver function tests, uric acid) must be conducted in all patients prior to initiating therapy. After initiation of Copegus therapy, laboratory evaluations should be performed at 2 and 4 weeks of therapy and periodically thereafter as clinically appropriate. 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 are:

- haemoglobin ≥ 120 g/L (females); ≥ 130 g/L (males)
- platelets ≥ 90 x 10⁹/L
- absolute neutrophil count (ACN) ≥ 1.5 x 10⁹/L
- TSH and T₄ within normal limits or adequately controlled thyroid function
- for HIV–HCV co-infected patients: CD4+ ≥ 200/mcl or CD4+ ≥ 100 mcl to < 200/mcl and HIV-1 RNA < 5000 copies/mL using Amplicor HIV-1 Monitor Test, v 1.5.

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.

Please refer to peginterferon alfa-2a or interferon alfa-2a prescribing information for additional information.

Interactions 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 as monotherapy or in combination with peginterferon alfa-2a or interferon alfa-2b.

Any potential for interactions may persist for up to 2 months (5 half lives for ribavirin) after cessation of Copegus therapy due to the long half-life.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that ribavirin induces liver enzymes. Therefore, there is a minimal potential for P450 enzyme-based interactions.

Antacid

The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid containing magnesium, aluminium and methicone; AUC_{0-∞} 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.

From a 12 week pharmacokinetic substudy examining the effects of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine, zidovudine or stavudine), there was no evidence of interaction observed in 47 HIV–HCV co-infected patients. Plasma exposure to ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).

Didanosine (ddl)

Ribavirin potentiated the antiretroviral effect of didanosine (ddl) *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 ddl might increase the risk of adverse reactions related to ddl (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 ddl in patients with HIV disease did not result in further reductions in viraemia or an increase in adverse reactions. Plasma pharmacokinetics of ddl were not significantly affected by concomitant ribavirin in this study, although intracellular ddATP was not measured.

Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactaemia/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.

In individual cases where the benefit of administering ribavirin 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 medicines should be stopped (see Warnings and Precautions).

Use in Special Populations

Use in Pregnancy – Category X

Copegus must not be used by women who are pregnant or by men whose female partners are pregnant.

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

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. Therefore, men must be instructed to use a condom to minimise delivery of ribavirin to their partners. Male patients and their female partners of childbearing age must be counselled to use 2 forms of effective contraception during treatment with Copegus and for 6 months after treatment has been concluded. Women must have a negative pregnancy test before therapy is started.

Nursing mothers

It is not known whether Copegus is excreted in human milk. Because of the potential for adverse reactions in nursing infants, a decision should be made either to discontinue nursing or not to initiate therapy.

Effects on Ability to Drive and Use Machines

Copegus has no or negligible influence on the ability to drive or operate machinery; however, interferon alfa-2a or peginterferon alfa-2a used in combination therapy may have an effect. Thus, patients who develop fatigue, somnolence, or confusion during treatment must be cautioned to avoid driving or operating machinery.

Undesirable Effects

Experience from clinical trials

The types and frequency of adverse events with combination therapy are consistent with the known safety profile of interferon alfa-2a or peginterferon alfa-2a and the undesirable effects associated with ribavirin.

Chronic hepatitis C

Treatment naïve patients

In comparison to 48 weeks of treatment with Copegus 1000/1200 mg and peginterferon alfa-2a 180 mcg, reducing treatment duration to 24 weeks and Copegus dose to 800 mg resulted in reductions in serious adverse events (11% vs 3%), premature withdrawals for safety reasons (13% vs 5%), and the need for Copegus dose modification (39% vs 19%).

Prior treatment non-responder patients

In study MV17150 the frequency of withdrawal from Pegasys treatment was 12% and Copegus treatment was 13% due to adverse events or laboratory abnormalities, for patients in the 72 week arms. In comparison, in 48 week treatment arms, 6% withdrew from Pegasys and 7% withdrew from Copegus treatment. Similarly for patients with cirrhosis, withdrawal rates from Pegasys and Copegus treatment were higher in the 72 week treatment arms, (13% and 15%) compared with the 48 week arms (6% and 6%). Patients who withdrew from previous therapy due to haematological toxicity were excluded from enrolling in this trial.

In the HALT C study, patients with advanced fibrosis or cirrhosis (Ishak score of 3 – 6) were enrolled with baseline platelet counts as low as $50 \times 10^9/L$ and treated for 48 weeks. Due to a high prevalence of the advanced cirrhosis/fibrosis state and the low baseline platelet counts among patients in this study, the frequency of haematologic lab abnormalities in the first 20 weeks of the trial were as follows: haemoglobin $< 100 \text{ g/L}$, 26.3%; absolute neutrophil count (ANC) $< 0.75 \times 10^9/L$, 30%; and platelet $< 50 \times 10^9/L$, 13% (see Warnings and Precautions).

HIV–HCV co-infection

In study NR15961, 180 mcg with and without 800 mcg Copegus in HIV-HCV co-infected patients, the clinical adverse events reported on peginterferon alfa-2a, alone or in combination with Copegus, were similar to that observed in HCV mono-infected patients. Limited safety data ($n = 51$) is available in co-infected patients with CD4+ cell counts $< 200/\text{mcl}$. In study NR 15961, the incidence of withdrawal from treatment for clinical adverse events, laboratory abnormalities or AIDS-defining events was 16% for peginterferon alfa-2a monotherapy, and 15% for peginterferon alfa-2a in combination with Copegus 800 mg, given for 48 weeks. Respectively, 4% or 3% of patients required discontinuation of peginterferon alfa-2a or peginterferon alfa-2a /Copegus, due to blood and lymphatic system disorder adverse event. In combination therapy, peginterferon alfa-2a dose modification occurred in 39%, and Copegus dose modification occurred in 37%, of the co-infected patients. Serious adverse events were reported in 21% and 17% of those receiving peginterferon alfa-2a monotherapy or in combination with Copegus, respectively.

Peginterferon alfa-2a containing treatment was associated with an on-treatment reduction in absolute CD4+ cell count without a reduction in CD4+ cell percentage. CD4+ cell count indices returned to baseline values during the follow-up period of the study. Peginterferon alfa-2a containing treatment had no apparent negative impact on the control of HIV viraemia during therapy or follow-up.

Study NV18209 compared 48 weeks of treatment with either Pegasys 180 mcg plus ribavirin 1000 or 1200 mg or Pegasys 180 mcg plus ribavirin 800 mg in interferon-naïve patients with HIV-HCV co-infected patients (HCV genotype 1 virus). 275 patients received the ribavirin 1000/1200 mg regime and 135 patients received the 800 mg regime. 80% of patients were male, median age 46 years, 64% Caucasian and 30% non-Hispanic African Americans. Over half of the patients in both treatment groups prematurely withdrew from either treatment and from either treatment group for safety (12 – 13%) or non-safety reasons (40 – 45%). The primary non-safety reason for premature withdrawal was insufficient therapeutic response (25 – 26%). The incidence of withdrawal for safety reasons was 12% (abnormal laboratory tests 4%, adverse events 8 – 9%). The incidence of adverse reactions of $\geq 10\%$ of patients in study NV18209 were similar to those within Table 5 for HIV-HCV co-infected patients, with no increased frequency for Pegasys plus ribavirin 1000/1200 mg compared with Pegasys plus ribavirin 800 mg except for anaemia (see Laboratory Test Values).

Table 5 shows those undesirable effects occurring in $\geq 10\%$ of HCV patients, as well as in HIV-HCV co-infected patients, who have received different treatment regimens of Copegus in combination with peginterferon alfa-2a. Adverse events reported in patients receiving ribavirin in combination with alpha interferon are essentially the same as those reported for Copegus in combination with peginterferon alfa-2a.

Table 5 Adverse Reactions (≥ 10% Incidence in Any Treatment Group)

	HCV (treatment naïve)		HIV – HCV (treatment naïve)	HCV (prior treatment non-responder)
	Copegus 800 mg & Peginterferon alfa-2a 180 mcg (NV 15492) 24 weeks	Copegus 1000 or 1200 mg & Peginterferon alfa-2a 180 mcg (NV 15801 + NV 15942) 48 weeks	Copegus 800 mg & Peginterferon alfa-2a 180 mcg (NR 15961) 48 weeks	Copegus 1000 or 1200 mg & Peginterferon alfa-2a 180 mcg (MV17150) 72 weeks
	<i>n</i> = 207	<i>n</i> = 887	<i>n</i> = 288	<i>n</i> = 156
Body System	%	%	%	%
Metabolism & nutrition disorders				
Anorexia	20	27	23	15
Weight decrease	2	7	16	9
Psychiatric disorders				
Insomnia	30	32	19	29
Irritability	28	24	15	17
Depression	17	21	22	16
Concentration impairment	8	10	2	5
Nervous system disorders				
Headache	48	47	35	32
Dizziness	13	15	7	10
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	11	13	7	11
Cough	8	13	3	17
Gastrointestinal disorders				
Nausea	29	28	24	24
Diarrhoea	15	14	16	13
Abdominal pain	9	10	7	9
Skin and subcutaneous tissue disorders				
Alopecia	25	24	10	18
Pruritus	25	21	5	22
Dermatitis	15	16	1	1
Dry skin	13	12	4	17
Musculoskeletal, connective tissue and bone disorders				
Myalgia	42	38	32	22
Arthralgia	20	22	16	15
General disorders and administration site conditions				
Fatigue	45	49	40	36
Pyrexia	37	39	41	20
Rigors	30	25	16	12
Injection site reaction	28	21	10	12

Asthenia	18	15	26	30
Pain	9	10	6	6

Undesirable effects reported in $\geq 1\%$ but $< 10\%$ on peginterferon alfa-2a/Copegus combination or peginterferon alfa-2a monotherapy in HCV and HIV–HCV patients were:

Infections and infestations: herpes simplex, URI infection, bronchitis, oral candidiasis

Blood and the lymphatic system disorders: lymphadenopathy, anaemia, thrombocytopenia

Endocrine disorders: hypothyroidism, hyperthyroidism

Neuropsychiatric: memory impairment, taste disturbance, paraesthesia, hypoesthesia, tremor, weakness, emotional disorders, mood alteration, nervousness, aggression, libido decreased, migraine, somnolence, hyperesthesia, nightmares, syncope, anxiety

Eye disorders: vision blurred, xerophthalmia, eye inflammation, eye pain

Ear and labyrinth disorders: vertigo, earache

Cardiac disorders: palpitations, oedema peripheral, tachycardia

Vascular disorders: flushing

Respiratory, thoracic and mediastinal disorders: sore throat, rhinitis, nasopharyngitis, sinus congestion, dyspnoea exertional, epistaxis

Gastrointestinal disorders: vomiting, dyspepsia, flatulence, dry mouth, mouth ulceration, gingival bleeding, stomatitis, dysphagia, glossitis

Skin and subcutaneous tissue disorders: skin disorder, rash, eczema, psoriasis, urticaria, photosensitivity reaction, sweating increased, night sweats

Musculoskeletal, connective tissue and bone disorders: bone pain, back pain, neck pain, muscle cramps, muscle weakness, musculoskeletal pain, arthritis

Reproductive system and breast disorders: impotence

General disorders and administration site conditions: influenza-like illness, malaise, lethargy, hot flushes, chest pain, thirst

Other adverse reactions reported in $\geq 1\%$ to $\leq 2\%$ of HIV-HCV patients receiving peginterferon alfa-2a/Copegus combination included: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

As with other alfa interferon therapies, uncommon to rare cases of the following serious adverse events have been reported in patients receiving peginterferon alfa-2a/Copegus combination or peginterferon alfa-2a monotherapy during clinical trials: lower respiratory tract infection, skin infection, otitis externa, endocarditis, suicide, substance overdose, hepatic dysfunction, fatty liver, cholangitis, malignant hepatic neoplasm, peptic ulcer, gastrointestinal bleeding, pancreatitis,

arrhythmia, atrial fibrillation, pericarditis, autoimmune phenomena (e.g., ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE), myositis, peripheral neuropathy, sarcoidosis, interstitial pneumonitis with fatal outcome, pulmonary embolism, corneal ulcer, coma and cerebral haemorrhage, TTP, psychotic disorder and hallucination.

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 Special dosage instructions).

Haemolysis is the defining toxicity of ribavirin therapy. A decrease in haemoglobin levels to < 100 g/L 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 < 100 g/L. 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.

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 $0.5 \times 10^9/L$ was observed in 13% and 11% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Decrease in platelets below $50 \times 10^9/L$ was observed in 10% and 8% of patients receiving peginterferon alfa-2a monotherapy and combination therapy, respectively. Anaemia (haemoglobin < 100 g/L) was reported in 7%, 14% and 28% of HIV-HCV co-infected patients treated with peginterferon alfa-2a monotherapy or in combination therapy with ribavirin 800 mg and 1000/1200 mg respectively in studies NR15961 and NV18209.

Please refer to the peginterferon alfa-2a or interferon alfa-2a prescribing information for additional information.

Post marketing

During the post-marketing period, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, pure red cell aplasia (PRCA) and homicidal ideation have been reported very rarely with combination therapy of peginterferon alfa-2a and ribavirin.

Dehydration has been reported rarely with Copegus and peginterferon alfa-2a combination therapy.

Rarely, alpha interferon including peginterferon alfa-2a, used in combination with ribavirin, may be associated with pancytopenia, and very rarely, aplastic anaemia has been reported.

As with other alfa interferons, serous retinal detachment has been reported with Copegus and peginterferon alfa-2a combination therapy.

As with other alfa interferons, liver and renal graft rejections have been reported with peginterferon alfa-2a, alone or in combination with Copegus.

Overdosage

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 cases ribavirin was administered intravenously. Ribavirin is not effectively removed by haemodialysis.

Pharmacological Properties and Effects

Pharmacodynamic Properties

Mechanism of action

Ribavirin is a synthetic nucleoside analogue that shows in-vitro activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with alpha interferon or peginterferon alfa-2a exerts its effects against HCV is unknown.

Oral formulations of ribavirin monotherapy have been investigated as therapy for CHC 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.

Efficacy/clinical studies

Copegus in combination with peginterferon alfa-2a

Chronic hepatitis C: naïve patients

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 CHC infection.

Study NV15801 (1121 patients treated) compared the efficacy of 48 weeks of treatment with peginterferon alfa-2a (180 mcg once weekly) and Copegus (1000/1200 mg daily) with either peginterferon alfa-2a monotherapy or combination therapy with interferon alfa-2b and ribavirin. The combination of peginterferon alfa-2a and Copegus was significantly more efficacious than the combination of interferon alfa-2b and ribavirin or peginterferon alfa-2a monotherapy (see Table 6).

Study NV15942 (1284 patients treated) compared the efficacy of two durations of treatment (24 weeks with 48 weeks) and two dosages of Copegus (800 mg with 1000/1200 mg).

In patients infected with genotype 1, the sustained virological response (SVR) was higher after 48 weeks of treatment than after 24 weeks ($p = 0.001$) and with the higher dose of Copegus ($p = 0.005$). However, for patients infected with genotype 2/3 there was no statistically significant difference between 48 and 24 weeks of treatment and between the low and high dose of Copegus (see Table 7). These patterns of response were not influenced by viral load or presence/absence of cirrhosis, therefore treatment recommendations are independent of these baseline

characteristics. Virological response was defined as undetectable HCV RNA as measured by the COBAS AMPLICOR™ HCV Test, version 2.0 (limit of detection 100 copies/mL equivalent to 50 IU/mL) and sustained response as one negative sample approximately 6 months after the end of therapy.

Table 6 Virological Response in the Overall Population (including non-cirrhotic and cirrhotic patients)

	Study NV15942	Study NV15801	
	Copegus 1000/1200 mg & Peginterferon alfa-2a 180 mcg (n = 436) 48 weeks	Copegus 1000/1200 mg & Peginterferon alfa-2a 180 mcg (n = 453) 48 weeks	Ribavirin 1000/1200 mg & Interferon alfa-2b 3 MIU (n = 444) 48 weeks
Response at end of treatment	68%	69%	52%
Overall sustained response	63%	54%*	45%*

* 95% CI for difference: 3% to 16% *p*-value (stratified Cochran-Mantel-Haenszel test) = 0.003

Table 7 SVR 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

Chronic hepatitis C: prior treatment non-responder patients
Study MV17150

In study MV17150, patients who were previous non-responders to peginterferon alfa-2b plus ribavirin therapy were randomised to four different treatments: Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 60 weeks; Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 36 weeks; Pegasys 180 mcg/week for 72 weeks; or Pegasys 180 mcg/week for 48 weeks. All patients received Copegus (1000 or 1200 mg/day) in combination with Pegasys. The end-of-treatment (EOT) virological response and SVR following the 24 week treatment-free period comparing duration of therapy or Pegasys induction dosing are summarised in Table 8. The SVRs following the 24 week treatment-free period from a pooled analysis comparing duration of therapy or Pegasys induction dosing are summarised in Table 9.

Table 8 EOT Virological Response and SVR in Previous Peginterferon alfa-2b/Ribavirin Non-responders

Study MV17150				
	Induction dosing 72 week treatment	Induction dosing 48 week treatment	Standard dosing 72 week treatment	Standard dosing 48 week treatment
	Pegasys 360 mcg 12 weeks then 180 mcg 60 weeks + Copegus 1000/1200 mg	Pegasys 360 mcg 12 weeks then 180 mcg 36 weeks + Copegus 1000/1200 mg	Pegasys 180 mcg 72 weeks + Copegus 1000/1200 mg	Pegasys 180 mcg 48 weeks + Copegus 1000/1200 mg
	<i>n</i> = 317	<i>n</i> = 156	<i>n</i> = 156	<i>n</i> = 313
EOT	31%	33%	31%	28%
SVR	16% ^{#*}	7% [§]	14%	9%

[#] A vs. B: 95% confidence interval of 1.36 to 5.67; odds ratio 2.77; *p*-value 0.0036

[§] B vs. C: 95% confidence interval of 0.23 to 1.03; odds ratio 0.49; *p*-value 0.0494

*A vs. D: 95% confidence interval of 1.21 to 3.31; odds ratio 2.0; *p*-value 0.0060

Table 9 SVR Rates in Previous Peginterferon alfa-2b/Ribavirin Non-responders: Pooled Treatment Comparisons

Study MV17150 (pooled groups)				
	72 week Groups	48 week Groups	360 mcg Groups	180 mcg Groups
	360 mcg 12 weeks then 180 mcg 60 weeks & 180 mcg 72 weeks	360 mcg 12 weeks then 180 mcg 36 weeks & 180 mcg 48 weeks	360 mcg 12 weeks then 180 mcg 60 weeks & 360 mcg 12 weeks then 180 mcg 36 weeks	180 mcg 72 weeks & 180 mcg 48 weeks
	(<i>n</i> = 473)	(<i>n</i> = 469)	(<i>n</i> = 473)	(<i>n</i> = 469)
SVR	16%*	8%*	13%	10%

* 95% confidence interval of 1.40 to 3.52; odds ratio 2.22; *p*-value 0.00061

The SVR rate after 72 weeks treatment was superior to that after 48 weeks. Differences in SVR based on treatment duration and demographics found in study MV17150 are displayed in Table 10.

Table 10 SVR Rates after Treatment with Pegasys and Copegus Combination Therapy in Non-responders to Previous Treatment with Peginterferon alfa-2b/Ribavirin

	Peginterferon alfa-2b/ribavirin Non-responders Re-treated for 48 weeks % SVR (responders/total)	Peginterferon alfa-2b/ribavirin Non-responders Re-treated for 72 weeks % SVR (responders/total)
Overall SVR for prior non-responder patients	8% (38/469)	16% (74/473)
Genotype 1/4	7% (33/450)	15% (68/457)
Genotype 2/3	25% (4/16)	33% (5/15)
Genotype		
1	7% (31/426)	14% (60/430)
2	0% (0/4)	33% (1/3)
3	33% (4/12)	33% (4/12)
4	8% (2/24)	30% (8/27)
Baseline Viral Load		
HVL (> 800 000 IU/mL)	7% (25/363)	12% (46/372)
LVL (≤ 800 000 IU/mL)	13% (11/84)	31% (27/86)

HVL = high viral load; LVL = low viral load

HALT-C study

In the HALT-C study, patients with CHC and advanced fibrosis or cirrhosis who had not responded to previous treatment with interferon alfa or peginterferon alfa monotherapy or combination ribavirin therapy were treated with Pegasys 180 mcg/week and Copegus 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on Pegasys plus Copegus combination therapy for a total of 48 weeks and were then followed for 24 weeks after the EOT. The SVR rates varied depending upon the previous treatment regimen. Treatment outcome was poorest among patients who were non-responders to peginterferon in combination with ribavirin, identifying the most difficult to treat subpopulation of non-responder patients. The SVR in this treatment arm of the HALT-C study was comparable with the rate observed in the 48 week treatment arms of study MV17150. Despite higher SVR rates in non-responders to interferon or peginterferon monotherapy, efficacy in these less difficult to treat non-responders remains substantially lower than what is achievable in treatment-naïve patients (see Table 11).

Table 11 SVR Rates by Treatment Duration and Non-responder Population

Treatment Duration	HALT-C Study				Study MV17150
	Interferon % SVR (responders/total)	Peginterferon % SVR (responders/total)	Interferon plus Ribavirin % SVR (responders/total)	Peginterferon plus Ribavirin % SVR (responders/total)	Peginterferon plus Ribavirin % SVR (responders/total)
48 weeks	27% (70/255)	34% (13/38)	13% (90/692)	11% (7/61)	8% (38/469)
72 weeks	-	-	-	-	16% (74/473)

Chronic hepatitis C: prior treatment relapser patients

In a study in predominantly genotype 1 CHC patients who had relapsed after 48 weeks of combination treatment with peginterferon alfa-2 plus ribavirin, patients were treated for 72 weeks with the combination of either Pegasys 180 mcg/week plus weight-based Copegus daily or consensus interferon (9 mcg) daily plus weight-based Copegus daily. The SVR was 42% for patients treated with Pegasys and Copegus combination therapy for 72 weeks.

In an open-label, study in genotype 2 and 3 CHC patients who relapsed after treatment for 24 weeks with Pegasys and Copegus combination therapy, patients were treated with Pegasys 180 mcg/week and Copegus 1000 or 1200 mg (by weight) daily combination therapy for 48 weeks and then followed treatment-free for 24 weeks. The SVR rate was 64%.

HIV-HCV co-infection

In study NR15961, 860 HIV-HCV co-infected patients were randomised and treated with peginterferon alfa-2a 180 mcg/week and placebo, peginterferon alfa-2a 180 mcg/week and ribavirin 800 mg/day or interferon alfa-2a 3 MIU three times weekly and ribavirin 800 mg/day for 48 weeks followed by a 24 week treatment free follow-up. The SVR for the three treatment groups are summarised for all patients and by genotype in Table 12.

Table 12 SVR in HIV-HCV Co-infected Patients (Study NR15961)

	Peginterferon alfa-2a 180 mcg + placebo 48 weeks	Peginterferon alfa-2a 180 mcg + Copegus 800 mg 48 weeks	Interferon alfa-2a 3MIU + Copegus 800 mg 48 weeks
All patients	20% (58/286)*	40% (116/289)*	12% (33/285)*
Genotype 1	14% (24/175)	29% (51/176)	7% (12/171)
Genotype 2/3	36% (32/90)	62% (59/95)	20% (18/89)

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

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared Pegasys 180 mcg/week and either ribavirin 800 mg or 1000 mg (<75 kg)/1200 mg (≥75 kg) daily for 48 weeks. The results are reported in Table 13 and showed that the study was not powered for efficacy considerations.

Table 13 SVR in HIV-HCV Co-infected Patients (Study NV18209)

	Pegasys 180 mcg with Copegus 800 mg 48 weeks (n = 138)	Pegasys 180 mcg with Copegus 1000/1200 mg 48 weeks (n = 277)
Completed	55/138 (40%)	119/277 (43%)
% SVR (responders/total)	19% (26/138)	22% (60/277)

Odds Ratio (95% CI) = 1.17 (0.69 – 1.98), p-value = 0.56

The safety profiles in both ribavirin groups were consistent with the known safety profile of Pegasys 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 naïve (previously untreated) and relapsed patients who had virologically, biochemically and histologically documented CHC. 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.

Pharmacokinetic Properties

Absorption

Ribavirin is absorbed rapidly following oral administration of a single dose of Copegus (median T_{max} = 1 - 2 h). The mean terminal phase half-life of ribavirin following single doses of Copegus range from 140 – 160 h. 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_{0-12h} following single doses of 200 – 1200 mg ribavirin. Mean apparent oral clearance of ribavirin following single 600 mg doses of Copegus ranges from 22 – 29 L/h. Volume of distribution is approximately 4500 L following administration of Copegus. Ribavirin does not bind to plasma proteins.

Food effect

The bioavailability of a single oral 600 mg dose Copegus was increased by coadministration of a high fat meal. The ribavirin exposure parameters of $AUC_{(0-192h)}$ and C_{max} increased by 42% and 66%, respectively, when Copegus was taken with a high fat breakfast compared to being taken in

the fasted state. The clinical relevance of results from this single dose study is unknown. Ribavirin exposure after multiple dosing when taken with food was comparable in patients receiving peginterferon alfa-2a and Copegus and interferon alfa-2b and ribavirin. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food.

Distribution

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following a single oral dose of Copegus (intra-subject variability of $\leq 25\%$ 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.

Metabolism

Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway, 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and both its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally.

Upon multiple dosing, ribavirin accumulates extensively in plasma with a six-fold ratio of multiple-dose to single-dose AUC_{12h} based on literature data. Following oral dosing with 600 mg bd, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations of approximately 2200 ng/mL.

Elimination

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

Pharmacokinetics in special populations

Patients with 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.

Patients with moderate or severe renal impairment (creatinine clearance ≤ 50 mL/min) not undergoing long term haemodialysis did not tolerate 600 mg and 400 mg daily doses of Copegus, respectively and exhibited higher ribavirin plasma exposures compared to patients with normal renal function (creatinine clearance > 80 mL/min) receiving the standard dose of Copegus (see Special Dosage Instructions).

In a study of patients with ESRD undergoing long term haemodialysis, most of whom received haematopoietic growth factors, Copegus was safely administered at a dose of 200 mg daily. In this

study, ESRD patients undergoing long term haemodialysis who were administered a 200 mg daily dose exhibited ribavirin plasma exposures that were approximately 20% lower compared to patients with normal renal function receiving the standard 1000/1200 mg Copegus daily dose (see Special Dosage Instructions).

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. Patients not undergoing long term with moderate or severe renal impairment (creatinine clearance ≤ 50 mL/min) did not tolerate daily doses of 600 mg and 400 mg of Copegus, respectively. Despite reduced Copegus dosing in these patients, ribavirin plasma exposure (AUC) was found to be higher compared to patients with normal renal function (creatinine clearance > 80 mL/min) receiving the standard Copegus dose. Patients with ESRD undergoing long term haemodialysis tolerated 200 mg daily doses of Copegus and exhibited mean ribavirin exposure (AUC) approximately 80% of the value found in patients with normal renal function (see Special Dosage Instructions). Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%.

Patients with hepatic dysfunction

Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction are similar to those of normal controls.

Elderly patients (≥ 65 years of age)

Specific pharmacokinetic evaluations for elderly subjects have not been performed. However, in a 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

Specific pharmacokinetic studies have not been fully evaluated in patients under the age of 18 years. Copegus in combination with peginterferon alfa-2a or interferon alfa-2a is indicated for the treatment of CHC only in patients 18 years of age or older.

Race

A pharmacokinetic study in 42 subjects demonstrated there is no clinically significant difference in ribavirin pharmacokinetics among Black ($n = 14$), Hispanic ($n = 13$) and Caucasian ($n = 15$) subjects.

Preclinical Safety

Carcinogenicity

In a p53 (+/-) mouse carcinogenicity study and a rat 2-year carcinogenicity study at doses up to the maximum tolerated doses of 100 mg/kg/day and 60 mg/kg/day, respectively, ribavirin was not oncogenic. On a body surface area basis, these doses are approximately 0.5 and 0.6 times the maximum recommended human 24 hour dose of ribavirin.

Impairment of fertility

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.

Other

Erythrocytes are a primary target of toxicity for ribavirin in animal studies. Anaemia occurs shortly after initiation of dosing, but is rapidly reversible upon cessation of treatment.

Genotoxicity studies have demonstrated that ribavirin does exert some genotoxic activity. Ribavirin was active in an *in vitro* Transformation Assay. Genotoxic activity was observed in-vivo mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. The potential of carcinogenic risk to humans cannot be excluded.

Administration of ribavirin and peginterferon alfa-2a in combination did not produce any unexpected toxicity in monkeys. The major treatment-related change was reversible mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

Pharmaceutical Particulars

Storage

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

Store below 30 °C.

The tablets should not be broken or crushed.

Since ribavirin is considered a potential teratogen, caution should be observed in handling broken tablets.

Special Instructions for Use, Handling and Disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicines should be returned to a pharmacy for disposal.

Medicine Classification

Prescription medicine.

Packs

Copegus[®] 200 mg film-coated tablets are supplied in high density polyethylene (HDPE) bottles with a child-resistant polypropylene screw cap containing 112 or 168 tablets.

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