

# Data Sheet

## Roferon<sup>®</sup>-A RBV<sup>™</sup>

*Interferon alfa-2a 18 MIU in 0.6 mL solution for injection + ribavirin film-coated tablets 200 mg*

**Antiviral agent**

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### Pharmaceutical Form

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Roferon-A RBV is a combination pack product, containing Roferon<sup>®</sup>-A solution for injection and Copegus<sup>®</sup> film-coated tablets.

Roferon-A is supplied as a ready to use solution for multi-dose injection.

Copegus is supplied as a 200 mg oval shaped film-coated tablet for oral administration.

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### Qualitative and Quantitative Composition

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#### ***Roferon-A***

##### **Active ingredient**

Interferon alfa-2a.

Each multi-dose cartridge contains 18 MIU (million international units) interferon alfa-2a in 0.6 mL and is used in conjunction with the Roferon<sup>®</sup>-Pen for subcutaneous (SC) injection.

##### **Excipients**

Ammonium acetate, sodium chloride, benzyl alcohol 1% (as a preservative), polysorbate 80 with buffers of glacial acetic acid, sodium hydroxide to pH 5.0 and water for injection in a ready-to-use solution for injection. There are volume overages of approximately 20% to compensate for the volume which remains after administration.

##### **Appearance**

Clear, colourless to slightly yellowish aqueous solution.

#### ***Copegus***

##### **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.

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## Clinical Particulars

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### ***Therapeutic Indications***

Roferon-A RBV is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV RNA, including patients with compensated cirrhosis.

### ***Dosage and Administration***

#### **Standard dosage**

The efficacy of interferon alfa-2a in the treatment of hepatitis C is enhanced when combined with ribavirin.

The recommended dose of Roferon-A RBV depends on the patient's body weight (see Table 1), and whether the patient is naïve or relapsed.

Patients should be treated with Roferon-A RBV combination therapy 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).

#### ***Roferon-A dosage***

##### *Naïve Patients*

*Dosage:* Roferon-A 3 to 4.5 MIU 3 times per week by subcutaneous injection for a period of at least 6 months. Treatment should be continued for an additional 6 months in patients who have negative HCV RNA at month 6, and are infected with genotype 1 and have high pretreatment viral load.

Patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) do not generally become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

##### *Relapsed patients*

Roferon-A RBV is given for adult patients with chronic hepatitis C who have previously responded to interferon alfa monotherapy, but who have relapsed after treatment was stopped.

*Dosage:* Roferon-A: 4.5 MIU 3 times per week by subcutaneous injection for a period of 6 months.

## Copegus dosage

<b>Patient weight (kg)</b>	<b>Daily Copegus Dose</b>	<b>Duration of Treatment</b>	<b>Number of 200 mg Tablets</b>
< 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***

If severe adverse reactions or laboratory abnormalities develop during therapy with Roferon-A RBV, modify the dosages of each product (Roferon-A and/or Copegus) until the adverse reactions abate. If intolerance persists after Roferon-A RBV dose adjustment, discontinuation of one or both medicines may be necessary.

#### Roferon-A

If the severity of constitutional adverse reactions does not diminish on continued treatment (tachyphylaxis) at the recommended dose, or cannot be controlled by concomitant symptomatic medication or by administering Roferon-A in the evening, then the dose of Roferon-A should be reduced to a level which, in terms of adverse reactions, is considered acceptable by the patient and the physician. If severe adverse events occur, it is recommended that the dose should be reduced by 50% or that treatment should be temporarily discontinued. It is safe to recommence therapy at a reduced dosage.

Dosage should be modified to take into account the constitutional symptoms, the myelosuppressive effects or other clinical or laboratory test abnormalities caused by Roferon-A and concurrently administered medicines or the effects of previous x-irradiation therapy or chemotherapy which may have reduced bone marrow reserve. It is advised that the recommended doses should not be exceeded and that the dosage schedules should be followed.

#### Copegus

For management of treatment-emergent anaemia, the following guidelines were developed in clinical trials (see Table 2).

<b>Laboratory Values</b>	<b>Reduce Copegus dose to 600 mg/day* only if:</b>	<b>Discontinue Copegus if**:</b>
Haemoglobin: 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 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, Special populations; Use in renal impairment, Pharmacokinetics in special populations; Patients with renal impairment).

#### *Use in hepatic impairment*

No pharmacokinetic interaction appears between ribavirin and hepatic function. Therefore, no dose adjustment of Copegus is required in patients with hepatic impairment. However, the use of Roferon-A (interferon alfa-2a) is contraindicated in patients with decompensated liver disease.

#### *Use in the elderly ( $\geq 65$ 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 Roferon-A RBV combination therapy in these patients have not been evaluated. Treatment with Roferon-A RBV is not recommended for use in children and adolescents under the age of 18.

Furthermore, it should be noted that benzyl alcohol, which is an excipient in Roferon-A solution for injection, has rarely been associated with potentially fatal toxicities in neonates (see Contraindications).

## **Contraindications**

Roferon-A RBV is contraindicated in

- Patients with a history of hypersensitivity to recombinant interferon alfa-2a, ribavirin or any of the excipients in Roferon-A or Copegus (see Qualitative and Quantitative Composition).
- Women who are pregnant, or men whose female partners are pregnant.

- Patients with severe pre-existing cardiac disease or with any history of cardiac illness. No direct cardiotoxic effect has been demonstrated, but it is likely that acute, self-limiting toxicities (e.g. fever, chills) frequently associated with administration of Roferon-A may exacerbate pre-existing cardiac conditions.
- Severe renal, hepatic or myeloid dysfunction.
- Seizure disorders and/or compromised central nervous system function.
- Chronic hepatitis with advanced, decompensated hepatic disease.
- Chronic hepatitis patients who are being or have recently been treated with immunosuppressive agents, excluding short-term 'steroid withdrawal'.
- Patients with haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia).
- Neonates, children up to 3 years, and premature infants. Roferon-A solution for injection contains benzyl alcohol. There have been reports of permanent neuropsychiatric deficits and multiple system organ failure associated with benzyl alcohol.

## ***Warnings and Precautions***

### ***General***

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

Roferon-A RBV combination therapy should be administered under the guidance of a qualified physician. Roferon A RBV therapy may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of further therapy.

When mild to moderate renal, hepatic or myeloid dysfunction is present, close monitoring of these functions is required.

### ***Hepatic function***

In patients who develop evidence of hepatic decompensation during treatment, Roferon-A RBV combination therapy should be discontinued.

Caution is recommended when administering interferon alfa to chronic hepatitis patients with a history of autoimmune disease. Consequently, any patient developing liver function abnormalities during Roferon-A RBV treatment should be closely monitored and if necessary treatment should be discontinued. Use of alfa-interferons has been rarely associated with severe hepatic dysfunction and liver failure.

### ***Renal impairment***

Copegus therapy should not be initiated in patients with moderate to severe renal impairment (creatinine clearance  $\leq$  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 Roferon-A RBV, Copegus therapy should not be continued.

Copegus therapy may be initiated in patients with end-stage renal disease (ESRD) undergoing long term 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, 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 on long term haemodialysis receiving Copegus should be carefully monitored.

### ***Bone marrow suppression***

Extreme caution should be exercised when administering Roferon-A to patients with severe myelosuppression as interferon alfa has a suppressive effect on the bone marrow, leading to a fall in the white blood count, particularly granulocytes, platelet count and, less commonly, haemoglobin concentration. This can lead to an increased risk of infection or haemorrhage. It is important to monitor these events closely and perform a full blood count before, and at regular appropriate intervals during, Roferon-A RBV treatment.

### ***Infections***

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia. Serious infections (bacterial, viral, fungal) have been reported during treatment with alfa-interferons including Roferon-A. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

### ***Teratogenic risk***

Prior to initiation of treatment with Roferon-A RBV the physician must comprehensively inform the patient of the teratogenic risk of Copegus (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 (see Pregnancy and Lactation).

### ***For women of childbearing potential***

While taking Roferon-A RBV 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.

### ***Psychiatric***

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including Roferon-A. Depression, suicidal ideation, and suicide may occur in patients with and without previous psychiatric illness. Roferon-A should be used with caution in patients who report a history of depression and physicians should monitor all patients treated with Roferon-A for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of Roferon-A RBV combination therapy, and patients should report any sign or symptom of depression immediately. Psychiatric intervention and/or medicine discontinuation should be considered in such cases.

### ***Ophthalmologic***

As with other interferons, retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, retinal artery or vein thrombosis and optic neuropathy which may result in loss of vision, have been reported after treatment with interferon alfa-2a. Any patient complaining of decreased or loss of vision must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual examination prior to initiation of Roferon-A RBV

combination therapy is recommended in patients with diabetes mellitus or hypertension. Roferon-A RBV combination therapy should be discontinued in patients who develop new or worsening ophthalmologic disorders.

### ***Hypersensitivity***

Serious, acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchoconstriction and anaphylaxis) have been rarely observed during alfa interferon therapy, including interferon alfa-2a. If such a reaction develops during treatment with Roferon-A RBV combination therapy, discontinue treatment immediately and institute appropriate medical therapy immediately. 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 2). 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 significant or unstable disease. Cardiac status must be assessed before initiation of Roferon-A RBV therapy and monitored clinically during therapy. If there is any deterioration of cardiovascular status, ribavirin therapy should be stopped (see Dosage and Administration, Table 2). It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to and during the course of 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 ribavirin 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).

### ***Endocrine***

Hyperglycaemia has been observed rarely in patients treated with Roferon-A. Symptomatic patients should have their blood glucose measured and followed-up accordingly. Patients with diabetes mellitus may require adjustment of their antidiabetic regimen.

### ***Autoimmune***

The development of different auto-antibodies has been reported during treatment with alfa-interferons. Clinical manifestations of autoimmune disease during interferon therapy occur more frequently in subjects predisposed to the development of autoimmune disorders.

Use of alfa-interferons has been rarely associated with exacerbation or provocation of psoriasis.

In transplant patients (e.g. kidney or bone marrow), therapeutic immunosuppression may be weakened because interferons also exert an immunostimulatory action.

### ***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 Roferon-A RBV. After initiation of Roferon-A RBV 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 Roferon-A RBV combination therapy are:

- haemoglobin  $\geq 12$  g/dL(females);  $\geq 13$ g/dL (males)
- platelets  $\geq 90\ 000/\text{mm}^3$
- neutrophil count  $\geq 1500/\text{mm}^3$

## ***Interactions with other Medicinal Products and other Forms of Interaction***

### **Roferon-A**

Alfa-interferons may affect oxidative metabolism by reducing the activity of hepatic microsomal P450 cytochrome enzymes. This should be taken into account when prescribing concomitant therapy with medicines metabolised by this route. Reduced clearance of theophylline following the concomitant administration of alfa-interferons has been reported.

The neurotoxic, haematotoxic or cardiotoxic effects of previously or concurrently administered medicines may be increased by interferons. Interactions could occur following concurrent administration of centrally-acting medicines.

### **Copegus**

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;  $AUC_{0-\infty}$  decreased 14%. It is possible that the decreased bioavailability in this study was due to delayed transit of ribavirin or modified pH. This interaction is not considered to be clinically relevant.

### **Nucleoside analogues**

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

### **Didanosine (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, 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; Haemolysis and cardiovascular system).

## ***Use in Special Populations***

### **Pregnancy**

Roferon-A RBV combination therapy 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 for Copegus. 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. Roferon-A RBV combination 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 Roferon-A or 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.

The excipient benzyl alcohol can be transmitted via the placenta. The possibility of toxicity should be taken into account in premature infants after the administration of Roferon-A solution for injection immediately prior to birth or Caesarean section.

### ***Effects on Ability to Drive and Use Machines***

Depending on the dose and schedule as well as the sensitivity of the individual patient, Roferon-A may have an effect on reaction times which could impair certain operations, such as driving or operating machinery.

Patients who develop fatigue, somnolence, confusion or an effect on reaction times during Roferon-A RBV 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.

Table 3 shows those undesirable effects occurring in > 10% in 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 ribavirin in combination with peginterferon alfa-2a.

<b>Table 3 Adverse Reactions (<math>\geq 10\%</math> Incidence)</b>		
	<b>Copegus 800 mg + Peginterferon alfa-2a 180 mcg 24 weeks n = 207</b>	<b>Copegus 1000 or 1200 mg + Peginterferon alfa-2a 180 mcg 48 weeks n = 887</b>
<b>Body System</b>	<b>%</b>	<b>%</b>
<b>Metabolism &amp; nutrition disorders</b>		
Anorexia	20%	27%
<b>Psychiatric disorders</b>		
Insomnia	30%	32%
Irritability	28%	24%
Depression	17%	21%
Concentration impairment	8%	10%
<b>Nervous system disorders</b>		
Headache	48%	47%
Dizziness	13%	15%
<b>Respiratory, thoracic and mediastinal disorders</b>		
Dyspnoea	11%	13%
Cough	8%	13%
<b>Gastrointestinal disorders</b>		
Nausea	29%	28%
Diarrhoea	15%	14%
Abdominal pain	9%	10%
<b>Skin and subcutaneous tissue disorders</b>		
Alopecia	25%	24%
Pruritus	25%	21%
Dermatitis	15%	16%
Dry skin	13%	12%
<b>Musculoskeletal, connective tissue and bone disorders</b>		
Myalgia	42%	38%
Arthralgia	20%	22%
<b>General disorders and administration site conditions</b>		
Fatigue	45%	49%
Pyrexia	37%	39%
Rigors	30%	25%
Injection site reaction	28%	21%
Asthenia	18%	15%
Pain	9%	10%

Undesirable effects reported in  $\geq 1\%$  but  $< 10\%$  on peginterferon alfa-2a/ribavirin combination or peginterferon alfa-2a monotherapy 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

As with other alpha interferon therapies, uncommon to rare cases of the following serious adverse events have been reported in patients receiving peginterferon alfa-2a/ribavirin 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, cerebral haemorrhage, TTP, psychotic disorder and hallucination.

Rarely, alpha interferons including Roferon-A, used in combination with ribavirin, may be associated with pancytopenia, and very rarely, aplastic anaemia has been reported.

Also see the Warnings and Precautions section of the Copegus datasheet if interferon alfa-2a is to be administered in combination with Copegus in patients with chronic hepatitis C.

### **Laboratory values**

In clinical trials of peginterferon alfa-2a or interferon alfa-2a in combination with ribavirin, 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 < 10 g/dL was observed in up to 15% of patients treated for 48 weeks with ribavirin 1000/1200 mg in combination with peginterferon alfa-2a and up to 19% of patients in combination with interferon alfa-2a. When ribavirin 800 mg was combined with peginterferon alfa-2a for 24 weeks, 3% of patients had a decrease in haemoglobin levels to < 10 g/dL. It is not expected that patients will need to discontinue therapy because of decrease in 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.

### ***Post-marketing***

During the post-marketing period, erythema multiforme, Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported very rarely with combination therapy of peginterferon alfa-2a and ribavirin.

Dehydration has been reported rarely with combination therapy of Copegus and alfa interferons.

As with other alfa interferons, serous retinal detachment has been reported with Pegasys and Copegus combination therapy.

## ***Overdose***

There are no reports of overdosage with Roferon-A, but repeated large doses of interferon can be associated with profound lethargy, fatigue, prostration and coma. Such patients should be hospitalised for observation and appropriate supportive treatment given.

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.

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## **Pharmacological Properties and Effects**

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### ***Roferon-A***

#### **Pharmacodynamic properties**

##### ***Mechanism of action***

Roferon-A exerts its antiviral effects by inducing a state of resistance to viral infections in cells and by modulating the effector arm of the immune system to neutralise viruses or eliminate virus-infected cells. Several changes have been described in human tumour cells treated with Roferon-A: HT 29 cells show a significant reduction of DNA, RNA and protein synthesis. Roferon-A has been shown to exert antiproliferative activity against a variety of human tumours *in-vitro* and to inhibit the growth of some human tumour xenografts in nude mice. A limited number of human tumour cell lines grown *in-vivo* in immunocompromised nude mice have been tested for susceptibility to Roferon-A. *In-vivo*, the antiproliferative activity of Roferon-A has been studied in tumours including breast mucoid carcinoma and adenocarcinoma of the caecum, colon and prostate. The degree of antiproliferative activity is variable.

Roferon-A is effective in the treatment of patients with proven compensated chronic hepatitis B and C.

## **Pharmacokinetic properties**

### ***Absorption***

The apparent fraction of the dose absorbed after IM or SC injection is greater than 80%. After IM administration of 36 MIU, peak serum concentrations range from 1500 to 2580 pg/mL (mean: 2020 pg/mL) at a mean time to peak of 3.8 hours and after SC administration of 36 MIU from 1250 to 2320 pg/mL (mean: 1730 pg/mL) at a mean time to peak of 7.3 hours, respectively.

### ***Distribution***

The pharmacokinetics of Roferon-A in man are linear over a 3-198 MIU dose range. After IV infusion of 36 MIU in healthy subjects, the volume of distribution at steady state ranges from 0.22 to 0.75 L/kg (mean: 0.40 L/kg). Serum interferon alfa-2a concentrations show wide intrasubject variation in both healthy volunteers and patients with disseminated cancer.

### ***Metabolism and elimination***

Renal catabolism is the major pathway for Roferon-A elimination; biliary excretion and liver metabolism are minor pathways. In healthy man, interferon alfa-2a has an elimination half-life of 3.7-8.5 hours (mean: 5.1 hours) and a total body clearance of 2.14-3.62 mL/min/kg (mean: 2.79 mL/min/kg) after IV infusion of 36 MIU.

## ***Copegus***

### **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 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.

#### ***Efficacy/clinical studies***

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.

## **Pharmacokinetic properties**

### ***Absorption***

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  $AUC_{0-\infty}$  following single doses of 200-1200 mg ribavirin. Mean apparent oral clearance of ribavirin following single 600 mg doses of Copegus ranges from 22 to 29 litres/hour. Volume of distribution is approximately 4500 litres following administration of Copegus. Ribavirin does not bind to plasma proteins.

### ***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 and elimination***

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  $AUC_{12hr}$  based on literature data. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations of approximately 2200 ng/mL. 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 of 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.

### ***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 (see Pharmacokinetic Properties). Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of Roferon-A RBV combination therapy, preferably by estimating the patient's creatinine clearance.

Patients with moderate or severe renal impairment (creatinine clearance  $\leq$  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  $\leq$  50 mL/min, including patients with ESRD undergoing long term haemodialysis, exhibiting approximately 30% of the value found in patients with normal renal function. Patients not undergoing long term haemodialysis with moderate or severe renal impairment (creatinine clearance  $\leq$  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 ( $\geq$ 65 years of age)**

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

#### **Patients under the age of 18 years**

Specific pharmacokinetic studies have not been fully evaluated in patients under the age of 18 years. Copegus in combination with interferon alfa-2a is indicated for the treatment of chronic hepatitis C 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, respectively, 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.

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## Pharmaceutical Particulars

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### **Stability**

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

Roferon-A 18 MIU multi-dose cartridges should be used within 28 days of the first withdrawal.

### **Special Remarks**

#### **Special precautions for storage**

The Roferon-A RBV combination therapy pack should be stored at 2 - 8°C; do not freeze. Protect from light.

When the cartridge is installed in the Roferon Pen, or placed in the specially designed carrying case provided with the Pen, the Roferon-A multi-dose cartridge can be stored at or below 25°C for up to 28 days. However, where possible, cartridges should be stored in the refrigerator (2 - 8°C) and returned to the refrigerator after each injection. Never freeze a Pen or its case when containing a cartridge.



Copegus film-coated tablets do not need to be kept at 2 - 8°C. Once the Roferon-A RBV combination therapy pack has been started, the Copegus film-coated tablet pack may be removed and stored separately below 30°C.

### **Instructions for use, handling and disposal**

Roferon-A 18 MIU cartridges are for multi-dose and single-patient use only. They are to be used exclusively with the Roferon Pen injector device. PenFine® needles are recommended for use with the Pen/cartridge combination although other needle types may be used. A new, sterile needle must be used for each injection. Roferon-A cartridges should be used within 28 days after first withdrawal. The date of first use of the cartridge should be written on the sticker supplied with the cartridges and the sticker attached to the case containing the Roferon-Pen. Detailed instructions on how to use the Roferon-Pen are provided with the Pen pack.

Copegus tablets should not be broken or crushed. Since ribavirin is considered a potential teratogen, caution should be observed in handling broken tablets.

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## **Medicine Classification**

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Prescription medicine

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## **Packs**

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### **Roferon-A RBV Combination Therapy Starter Packs**

Each pack contains:

- 2 x Roferon-A 18 MIU cartridge 1's
- 1 x Copegus 200 mg film-coated tablets 168's
- 1 x Roferon Pen injector
- 1 x Penfine 10 mm 29 G needles 100's

### **Roferon-A RBV Combination Therapy Packs**

Each pack contains:

- 2 x Roferon-A 18 MIU cartridge 1's
- 1 x Copegus 200 mg film-coated tablets 168's

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## **Name and Address**

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## Date of Preparation

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