Roferon® A
Interferon alfa 2a

Antiviral and antineoplastic agent

1. PHARMACEUTICAL FORM
Roferon-A is supplied as a ready-to-use solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: interferon alfa-2a.

Interferon alfa-2a is produced biosynthetically using recombinant DNA technology, and is the product of a cloned human leukocyte interferon gene inserted into and expressed in *E. coli.*

Each prefilled syringe (for single-dose, s.c. injection) contains 3, 4.5, 6, or 9 MIU interferon alfa-2a in 0.5 ml.

3. CLINICAL PARTICULARS
3.1 Therapeutic Indications
Roferon-A is indicated for the treatment of:
Neoplasms of the lymphatic or hematopoietic system: hairy cell leukemia, cutaneous T-cell lymphoma, chronic myelogenous leukemia.

Solid neoplasms: AIDS-related Kaposi's sarcoma in patients without history of opportunistic infection, advanced renal cell carcinoma.

Viral diseases: Adult patients with chronic active hepatitis B who have markers for viral replication, i.e. those who are positive for HBV-DNA, DNA polymerase or HBeAg; adult patients with chronic hepatitis C (hepatitis non-A, non-B) who are positive for HCV antibodies and have elevated serum alanine aminotransferase (ALT) without liver decompensation (Child's class A).

The efficacy of interferon alfa-2a in the treatment of hepatitis C is enhanced when combined with ribavirin. Roferon-A should be given alone mainly in case of intolerance or contraindication to ribavirin.

3.2 Dosage and Method of Administration
3.2.1 Standard Dosage
Substitution of Roferon-A by any other biological similar medicinal product requires the consent of the prescribing physician.

Roferon-A should be administered by s.c. injection. Refer to the Copegus prescribing information when Roferon-A is used in combination with ribavirin.

3.2.2 Special Dosage Instructions
Hairy cell leukemia
Initial dosage: 3 MIU daily for 16-24 weeks. If intolerance develops, either the daily dose should be lowered to 1.5 MIU or the schedule changed to three times per week, or both.

Maintenance dosage: 3 MIU three times per week. If intolerance develops, the dose should be lowered to 1.5 MIU three times per week.

Duration of treatment: Patients should be treated for approximately 6 months before the physician decides whether to continue treatment in responding patients or to discontinue treatment in non-responding patients. Patients have been treated for up to 20 consecutive months. The optimal duration of Roferon-A treatment for hairy cell leukemia has not been determined.

Cutaneous T-cell lymphoma (CTCL)
Roferon-A may be active in patients with progressive cutaneous T-cell lymphoma and who are refractory to, or unsuitable for, conventional therapy.
Initial dosage: 3-18 MIU daily for a total of 12 weeks in patients aged 18 years or older. The recommended escalation schedule is as follows:
Days 1-3: 3 MIU daily
Days 4-6: 9 MIU daily
Days 7-84: 18 MIU daily

Maintenance dosage: The maximum dose acceptable to the patient, but not exceeding 18 MIU, three times weekly.

Duration of treatment: Patients should be treated for a minimum of 8 weeks, and preferably for at least 12 weeks, before the physician decides whether to continue treatment in responding patients or to discontinue treatment in non-responding patients. The minimum treatment duration in responding patients should be 12 months to maximise the chance of a complete and prolonged response. Patients have been treated for up to 40 consecutive months. The optimal duration of Roferon-A treatment for cutaneous T cell lymphoma has not been determined. Objective tumor responses have not been observed in approximately 40% of patients with CTCL.Partial responses are usually seen within 3 months and complete responses within 6 months, although it may occasionally take more than 12 months to achieve an optimum response.

Chronic myelogenous leukemia (CML)
Roferon-A is indicated for the treatment of patients with chronic phase Philadelphia-chromosome positive chronic myelogenous leukemia. It is still unknown whether Roferon-A can be considered as a treatment with a curative potential in this indication.

Roferon-A produces hematological remission in 60% of patients with chronic phase CML, independent of prior treatment. Two thirds of these patients have complete hematological responses as late as 18 months after treatment start.

In contrast to cytotoxic chemotherapy, interferon alfa-2a is able to generate sustained, ongoing cytogenetic responses beyond 40 months.

Dosage recommendation: 3-9 MIU daily in escalating doses for 8-12 weeks in patients aged 18 years or older. The recommended escalation schedule is as follows:
Days 1-3: 3 MIU daily
Days 4-6: 6 MIU daily
Days 7-84: 9 MIU daily

Duration of treatment: Patients should be treated for a minimum of 8 weeks, and preferably for at least 12 weeks, before the physician decides whether to continue treatment in responding patients or to discontinue treatment in patients not showing any changes in hematological parameters. In CML, responding patients should be treated until complete hematological response is achieved or for a maximum of 18 months. All patients with complete hematological responses should continue treatment with 9 MIU daily (optimum) or 9 MIU three times per week (minimum) in order to achieve a cytogenetic response in the shortest possible time. The optimal duration of Roferon-A treatment for chronic myelogenous leukemia has not been determined, although cytogenetic responses have been observed 2 years after treatment start. The safety, efficacy and optimal dosage of Roferon-A in children with CML have not yet been established.

AIDS-related Kaposi's sarcoma
Roferon-A is indicated for the treatment of patients with AIDS-related Kaposi's sarcoma in patients without history of opportunistic infection. The optimal dosage has not yet been well established.

Patients with AIDS-related Kaposi's sarcoma are more likely to respond to therapy if they have no history of opportunistic infection, no B symptoms (greater than 10% loss of body weight, fever ≥ 38°C with no identified source of infection or night sweats) and a baseline T4 lymphocyte count of greater than 200 cells/mm^3.

Initial dosage: 3 MIU daily, escalated to at least 18 MIU daily, and if possible to 36 MIU daily, for a total of 10-12 weeks in patients aged 18 years or older. The recommended escalation schedule is as follows:
Days 1-3: 3 MIU daily
Days 4-6: 9 MIU daily
Days 7-9: 18 MIU daily - and, if tolerated, increase to:
Days 10-84: 36 MIU daily

Maintenance dosage: The maximum dose acceptable to the patient, but not exceeding 36 MIU, three times weekly.

Patients with AIDS-related Kaposi's sarcoma treated with 3 MIU of Roferon-A daily have shown a lower response rate than those treated with the recommended dosage.

Duration of treatment: The evolution of lesions should be documented to determine response to therapy. Patients should be treated for a minimum of 10 weeks, and preferably for at least 12 weeks, before the physician decides whether to continue treatment in responding patients or to discontinue treatment in non-responding patients. Patients generally show evidence of response after approximately 3 months of therapy. Patients have been treated for up to 20 consecutive months. If a response occurs, treatment should continue at least until there is no further evidence of tumor. The optimal duration of Roferon-A treatment for AIDS-related Kaposi's sarcoma has not been determined.

Lesions of Kaposi's sarcoma frequently reappear when Roferon-A treatment is discontinued.

Advanced renal cell carcinoma
The highest tumor response rates have been observed in patients with recurrent or metastatic disease using either high-dose Roferon-A (36 MIU daily) as monotherapy or moderate-dose Roferon-A (18 MIU three times per week) combined with vinblastine, as compared with moderate-dose Roferon-A monotherapy given three times per week. Patients treated with low-dose Roferon-A (2 MIU/m^2 body surface area given daily) have shown no response to treatment. The combination of Roferon-A with vinblastine results in only small increases in the frequency of mild to moderate leukopenia and granulocytopenia compared with monotherapy.

a) Roferon-A monotherapy
Initial dosage: 3 MIU daily, escalated to at least 18 MIU daily and if possible 36 MIU daily, for a total of 8-12 weeks. The recommended escalation schedule is as follows:
Days 1-3: 3 MIU daily
Days 4-6: 9 MIU daily
Days 7-9: 18 MIU daily - and, if tolerated, increase to:
Days 10-84: 36 MIU daily

Maintenance dosage: The maximum dose acceptable to the patient, but not exceeding 36 MIU, three times weekly.

Duration of treatment: Patients should be treated for a minimum of 8 weeks, and preferably for at least 12 weeks, before the physician decides whether to continue treatment in responding patients or to discontinue treatment in non-responding patients. Patients have been treated for up to 16 consecutive months. The optimal duration of Roferon-A treatment for advanced renal cell carcinoma has not been determined.

b) Roferon-A with vinblastine
Therapy with Roferon-A in combination with vinblastine induces overall response rates of approximately 20%, delays disease progression, and prolongs overall survival in patients with advanced renal cell carcinoma.

Dosage recommendation: 3 MIU three times weekly for one week, 9 MIU three times weekly for the following week and 18 MIU three times weekly thereafter. Concomitant vinblastine should be given intravenously according to the manufacturer's instructions at a dose of 0.1 mg/kg once every 3 weeks.

If 18 MIU Roferon-A three times per week is not tolerable, the dose may be reduced to 9 MIU three times per week.

Treatment should be given for a minimum of three months, up to a maximum of 12 months or until the development of progressive disease. Patients who achieve a complete response may stop treatment three months after the response is established.

Chronic active hepatitis B
Roferon-A is indicated for the treatment of adult patients with chronic active hepatitis B who have markers for viral replication, i.e. those who are positive for HBV-DNA, DNA polymerase or HBeAg.

Dosage recommendation: The optimal treatment schedule of Roferon-A treatment for chronic active hepatitis B has not yet been established. The dose is usually 4.5 MIU three times per week for 6 months.
If markers for viral replication or HbeAg do not decrease after one month of therapy, the dose can be escalated. The dosage may be further adjusted to the patient's tolerance to the medication. If no improvement has been observed after 3-4 months of treatment, discontinuation of therapy should be considered.

Children: Up to 10 MIU/m2 has been safely administered to children with chronic hepatitis B. However, efficacy of therapy has not been demonstrated.

Efficacy in chronic hepatitis B patients co-infected with the human immunodeficiency virus (HIV) has not been demonstrated.

Chronic hepatitis C
Roferon-A is indicated for the treatment of adult patients with chronic hepatitis C who are positive for HCV antibodies and have elevated serum alanine aminotransferase (ALT) without liver decompensation (Child's class A). The efficacy of Roferon-A in the treatment of hepatitis C is enhanced when combined with ribavirin. Roferon-A should be given alone mainly in case of intolerance or contraindication to ribavirin.

This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alfa therapy and subsequently relapsed after treatment was stopped.

Roferon-A in combination with ribavirin
Dosage recommendation:
Treatment naïve patients: Roferon-A should be administered at a dose of 3 – 4.5 MIU three times per week for a period of 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.

Relapsed patients: Roferon-A should be administered at a dose of 4.5 MIU three times per week for a period of 6 months.

Treatment should be continued for an additional 6 months in patients who have negative HCV RNA at month 6, and are infected genotype 1 and have high pretreatment viral load.

For ribavirin dosage recommendation please refer to the Copegus prescribing information.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.
Patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) do generally not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Roferon-A monotherapy
Roferon-A monotherapy should be given mainly in case of intolerance or contraindication to ribavirin.

Dosage recommendation: 6 MIU three times per week for 3 months as induction therapy

Maintenance dosage: Patients whose serum ALT has normalized and/or HCV RNA has become undetectable require maintenance therapy with 3 MIU Roferon-A three times a week for an additional 6 months or longer to consolidate the complete response.

The optimal duration of therapy has not yet been determined but a therapy of at least 12 months is advised.

Patients whose serum ALT has not normalized should stop treatment.

Note: The majority of patients who relapse after adequate treatment do so within 4 months of ending treatment.

Contraindications

Roferon-A is contraindicated in

- Patients with a history of hypersensitivity to recombinant interferon alfa-2a or any component of the preparation.
- Patients with severe preexisting 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 preexisting cardiac conditions.
- Severe renal, hepatic or myeloid dysfunction.
- Seizure disorders and/or compromised central nervous system function.
- Chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis.
- Chronic hepatitis patients who are being or have recently been treated with immunosuppressive agents, excluding short-term 'steroid withdrawal'.
- CML patients with an HLA-identical relative who are potential candidates for allogeneic bone marrow transplantation in the immediate future.
- 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.

Ribavirin, given in combination with Roferon-A, must not be used in women who are pregnant. Please refer also to the approved ribavirin prescribing information.

3.3 Special Warnings and Special Precautions for Use

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file.

Roferon-A should be administered under the supervision of a qualified physician experienced in the management of the respective indication. Appropriate management of therapy and its complications is possible only when adequate diagnostic and treatment facilities are readily available.

Patients should be informed not only of the benefits of therapy but also that they will probably experience adverse reactions. Alfa interferons, including Roferon-A, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping Roferon-A therapy. Alfa interferons suppress bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pretreatment and monitored routinely during therapy. Alfa interferon therapy should be discontinued in patients who develop severe decreases in neutrophil (<0.5 x 10^9/L) or platelet counts (<25 x 10^9/L).

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

Hepatic function: 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 treatment should be closely monitored and if necessary treatment should be discontinued. Use of alfa-interferons have been rarely associated with severe hepatic dysfunction and liver failure.

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 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.

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 therapy, and patients should report any sign or symptom of depression immediately. Psychiatric intervention and/or drug 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 monotherapy or Roferon-A/ribavirin combination therapy is recommended in patients with diabetes mellitus or hypertension. Roferon-A or Roferon-A/ribavirin should be discontinued in patients who developed 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 either with Roferon-A or with Roferon-A/ribavirin, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Endocrine: Hyperglycemia 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. Autoimmune phenomena such as vasculitis, arthritis, hemolytic anemia, thyroid dysfunction and lupus erythematous syndrome have been observed rarely in patients receiving Roferon-A.

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. As with other alpha interferons, graft rejections have been reported in patients taking Roferon-A.

The use of Roferon-A in children is not recommended as safety and efficacy have not been established in children. Furthermore, Roferon-A solution for injection is not recommended for use in the newborn or children under the age of 2 years since it contains benzyl alcohol as a preservative.

Since there have been reports of permanent neuropsychiatric deficits and multiple system organ failure associated with benzyl alcohol, administration to neonates, and especially to premature infants, must be avoided.

3.4 Interactions with other Medical Products and other Forms of Interaction

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 drugs metabolised by

this route. Reduced clearance of theophylline following the concomitant administration of alfa-interferons has been reported.

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

Combination therapy with ribavirin: Also see ribavirin labeling if interferon alfa-2a is to be administered in combination with ribavirin in patients with chronic hepatitis C.

3.5 Pregnancy and Lactation

Men and women receiving Roferon-A should practice effective contraception. In pregnancy, Roferon-A should be administered only if the benefit to the woman justifies the potential risk to the fetus. Although animal tests do not indicate that Roferon-A is a teratogen, harm to the fetus from use during pregnancy cannot be excluded. When doses greatly in excess of the recommended clinical dose were administered to pregnant rhesus monkeys in the early to mid-fetal period, an abortifacient effect was observed.

It is not known whether Roferon-A is excreted in human milk. A decision must be taken whether to suspend breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

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 Cesarean section.

Roferon-A given in combination with ribavirin must not be used in pregnant women. Fertile women and partners of fertile women should not receive ribavirin combination therapy unless the patient and his/her partner are taking efficacious contraceptive measures. Also see ribavirin labeling if interferon alfa-2a is to be administered in combination with ribavirin in patients with chronic hepatitis C.

3.6 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.

3.7 Undesirable Effects

The following data on adverse reactions are based on information derived from the treatment of cancer patients with a wide variety of malignancies who were often refractory to previous therapy and suffering from advanced disease, patients with chronic hepatitis B and patients with chronic hepatitis C. Please refer also to the "Undesirable Effects" section of the Copegus prescribing information.

General symptoms. *Frequent*: Flu-like symptoms, e.g. fatigue, fever, chills, appetite loss, myalgia, headache, arthralgia and diaphoresis. These acute side-effects can usually be reduced or eliminated by concurrent administration of paracetamol and tend to diminish with continued therapy or dose moderation. Continuing therapy can lead to lethargy, weakness and fatigue.

Gastrointestinal tract. *Frequent:* About two thirds of cancer patients experienced anorexia and one half nausea. *Common:* Emesis, taste alterations, dry mouth, weight loss, diarrhea and mild or moderate abdominal pain. *Rare:* Constipation, flatulence, hypermotility, heartburn, reactivation of peptic ulcer, non-life-threatening gastrointestinal bleeding as well as pancreatitis.

Alterations of hepatic function. Uncommon: Elevation of ALT, alkaline phosphatase, lactate dehydrogenase and bilirubin, which generally did not require dose adjustment. *Rare:* In hepatitis B, changes in transaminases usually signal clinical improvement.

Central nervous system. Uncommon: Dizziness, vertigo, decreased mental status, forgetfulness, depression, drowsiness, confusion, behavioural disturbances, such as anxiety and nervousness, sleep disturbances. *Rare:* Suicidal ideation, suicide attempt, suicide. Severe somnolence, convulsions, coma, cerebrovascular adverse events and transient impotence.

Vision disorders. Uncommon: visual disturbance. *Rare:* ischaemic retinopathy. *Very rare:* retinopathy including retinal haemorrhages and cotton-wool spots, papilloedema, retinal artery and vein thrombosis and optic neuropathy.

Peripheral nervous system. Uncommon: Paresthesia, numbness, neuropathy, itching and tremor.

Cardiovascular and pulmonary systems. Common: Disorders were seen in about one fifth of cancer patients and consisted of transient hypotensive and hypertensive episodes, edema, cyanosis, arrhythmias, palpitations and chest pain. *Rare:* Coughing, mild dyspnea, pulmonary edema, pneumonia, congestive heart failure, cardiorespiratory arrest and myocardial infarction. Cardiovascular problems are very rarely seen in patients with hepatitis B.

Skin, mucous membranes and adnexa. *Common*: Mild to moderate alopecia occurred in up to one fifth of patients, but this was reversible on discontinuation of treatment. *Rare*: Re-exacerbation of herpes labialis, rash, pruritus, dry skin and mucous membranes, rhinorrhea and epistaxis.

Renal and urinary system. *Rare*: Decreased renal function; acute renal failure, mainly in cancer patients with renal disease and/or nephrotoxic comedications as concomitant risk factors; electrolyte disturbances, generally in association with anorexia or dehydration; proteinuria; increased cell count in sediment; elevations of BUN, serum creatinine and uric acid.

Hematopoietic system. Common: Transient leukopenia rarely requiring restriction of dosage, in myelosuppressed patients, thrombocytopenia and decreased hemoglobin. *Uncommon:* In non-myelosuppressed patients, thrombocytopenia. *Rare:* Decrease of hemoglobin and hematocrit. Recovery of severe hematological deviations to pretreatment levels usually occurred within 7-10 days after discontinuing Roferon-A treatment. *Very rare:* Idiopathic thrombocytopenic purpura (ITP).

Other. Rare: Hyperglycemia, diabetes mellitus, injection site reactions including, very rarely, necrotic site reactions, autoimmune phenomena, i.e. vasculitis, arthritis, hemolytic anemia, thyroid dysfunction and lupus erythematosus syndrome. *Very rare*: Asymptomatic hypocalcemia, sarcoidosis, hypertriglyceridemia / hyperlipidemia. Transient menstrual cycle irregularities including prolonged menstrual periods have been seen in rhesus monkeys administered doses greatly in excess of the recommended clinical dose.

Combination therapy with ribavirin: Also see the Warning and Special Precautions section of the Copegus prescribing information if interferon alfa-2a is to be administered in combination with ribavirin to patients with chronic hepatitis C.

Rarely, alpha interferons including Roferon-A, used in combination with ribavirin, may be associated with pancytopenia, and very rarely, aplastic anemia has been reported. *Anti-interferon antibodies*: Neutralizing antibodies to proteins may be formed in some subjects following homologous administration. Antibodies to all interferons, whether natural or recombinant, are therefore likely to be found in a certain proportion of patients. In certain clinical conditions (cancer, systemic lupus erythematosus, herpes zoster) antibodies to human leukocyte interferon may also occur spontaneously in patients who have never received exogenous interferons.

In clinical trials using lyophilized Roferon-A stored at 25°C, neutralizing antibodies to Roferon-A were detected in approximately one fifth of patients. There is no evidence in any clinical indication that the presence of such antibodies affects the response to Roferon-A. In hepatitis C, a trend has been seen for responding patients who develop neutralizing antibodies to lose response while still on treatment and to lose it earlier than patients who do not develop such antibodies. No other clinical sequelae of the presence of antibodies to Roferon-A have been documented.

No data on neutralizing antibodies yet exist from clinical trials using lyophilized Roferon-A or Roferon-A solution for injection stored at 4°C. In a mouse model, the relative immunogenicity of lyophilized Roferon-A increases with time when the material is stored at 25°C - no such increase in immunogenicity is observed when lyophilized Roferon-A is stored at the recommended temperature of 4°C.

As with other alpha interferons, graft rejections have been reported in patients taking Roferon-A

3.7.1 Post Marketing

The following adverse reactions have been identified during post-marketing use of Roferon-A. As these events are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency.
Immune System Disorders: as with other alpha interferons, graft rejections have been reported in patients taking Roferon-A
Psychiatric disorder: mania has been reported
Gastrointestinal disorders: hemorrhagic/ischemic colitis and ulcerative colitis have been reported
Respiratory, thoracic and mediastinal disorders: Pulmonary arterial hypertension (Frequency unknown)
Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection,cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

3.8 Overdose

There are no reports of overdosage, 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. Patients who experience severe reactions to Roferon-A will usually recover within days after discontinuation of therapy, given appropriate supportive care. Coma has been observed in 0.4% of cancer patients in clinical trials.

4. PHARMACOLOGICAL PROPERTIES AND EFFECTS

Roferon-A has been shown to possess many of the activities of the so-called natural human alfa-interferon preparations.

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. The essential mechanism for the antitumour action of Roferon-A is not yet known. However, several changes have been described in human tumor 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 tumors in vitro and to inhibit the growth of some human tumor xenografts in nude mice. A limited number of human tumor 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 tumors including breast mucoid carcinoma and adenocarcinoma of the cecum, colon and prostate. The degree of antiproliferative activity is variable.

Unlike other human proteins, many of the effects of interferon alfa-2a are partially or completely suppressed when it is tested in other animal species. However, significant antivaccinia virus activity is induced in rhesus monkeys pretreated with interferon alfa-2a.

4.1 Pharmacodynamic Properties

No information available.

4.2 Pharmacokinetic Properties

4.2.1 Absorption

The apparent fraction of the dose absorbed after i.m. or s.c. injection is greater than 80%. After i.m. 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 s.c. 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.

4.2.2 Distribution
The pharmacokinetics of Roferon-A in man are linear over a 3-198 MIU dose range. After i.v. 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.

4.2.3 Metabolism
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 i.v. infusion of 36 MIU.

4.2.4 Elimination
See 4.2.3

4.2.5 Pharmacokinetics in Special Populations
The pharmacokinetics of interferon alfa-2a after single i.m. doses in patients with disseminated cancer and chronic hepatitis B are similar to those in healthy volunteers. Dose-proportional increases in serum concentrations are observed after single doses of up to 198 MIU. There are no changes in the distribution or elimination of interferon alfa-2a during twice daily (0.5-36 MIU), once daily (1-54 MIU), or thrice weekly (1-136 MIU) dosing for up to 28 days.

I.m. administration of Roferon-A one or more times daily for up to 28 days has resulted in peak plasma concentrations two to four times greater than after single doses in some patients with disseminated cancer. However, multiple dosing has caused no changes in distribution or elimination parameters in any of the dosage regimens hitherto studied.

For other information on pharmacokinetic properties for ribavirin please refer to the prescribing information for Copegus.

5. PHARMACEUTICAL PARTICULARS
5.1 List of Excipients
Ammonium acetate
Sodium chloride
Benzyl alcohol
Polysorbate 80
Glacial acetic acid
Sodium hydroxide solution
Water for injections

5.2 Stability
This medicine should not be used after the expiry date (EXP) shown on the pack.
Cartridges should be used within 30 days of the first withdrawal.

5.3 Special Remarks
5.3.1 Special Precautions for Storage
Store at 2-8 °C; do not freeze. Store container in outer carton to protect from light.

5.4 Special Instructions for Use, Handling and Disposal
Disposal of syringes/sharps
The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:
- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider.

For home use, a puncture resistant container for the disposal of used syringes and needles should be supplied to the patients.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available in your location.

6. PACKS
Roferon-A solution, 3 MIU/0.5 ml prefilled syringes: 1
Roferon-A solution, 6 MIU/0.5 ml prefilled syringes: 1

Medicine: keep out of reach of children

Current at Feb 2017

Roche

Syringes:
Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel;
manufacturing site Kaiseraugst