Roferon®-A

Interferon alfa-2a

Composition

Active substance

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

Excipients

1 prefilled syringe contains: sodium chloride; ammonium acetate; polysorbate 80 (from genetically modified maize); preservative: benzyl alcohol 5.0 mg; water for injection q.s. 0.5 ml of solution.

1 cartridge contains: sodium chloride; ammonium acetate; polysorbate 80 (from genetically modified maize); preservative: benzyl alcohol 6.0 mg; water for injection q.s. 0.6 ml of solution.

Pharmaceutical Form and Quantity of Active Substance per Unit

Roferon-A is supplied as a solution for injection in:

prefilled syringes:	3 MIU/0.5 ml
	4.5 MIU/0.5 ml
	6 MIU/0.5 ml
	9 MIU/0.5 ml
and in a cartridge:	18 MIU/0.6 ml

Indications and Potential Uses

- Hairy cell leukemia
- Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)
- Chronic-phase chronic myelogenous leukemia
- AIDS-related Kaposi's sarcoma
- Adjuvant therapy of surgically resected malignant melanoma of AJCC stage II (Breslow tumour thickness >1.5 mm; no nodal or distant metastases)
- Advanced renal cell carcinoma in combination with vinblastine
- First-line treatment of nephrectomised patients with advanced and/or metastatic renal cell carcinoma in combination with bevacizumab

Chronic hepatitis C

Histologically proven chronic hepatitis C in adult patients with HCV antibodies, HCV RNA and elevated serum alanine aminotransferase (ALT) without liver decompensation.

The efficacy of interferon alfa-2a in the treatment of relapsed patients with chronic hepatitis C is increased by combination with ribavirin.

In combination therapy, please refer to the prescribing information for ribavirin.

For previously untreated (interferon-naive) patients only a small, open-label comparative study is available on combination with ribavirin.

Chronic hepatitis B

Roferon-A is indicated to increase the likelihood of seroconversion in Caucasians with chronic active hepatitis B without liver decompensation. Chronic active hepatitis B must be confirmed by liver biopsy, raised transaminase levels (>6 months) and markers of viral replication (positive for HBV DNA and HBeAg). Positive effects on the development of liver cirrhosis or hepatocellular carcinoma have not been demonstrated.

Dosage and Administration

The prefilled syringes and the cartridges for use with the Roferon-Pen are designed for subcutaneous (s.c.) administration only.

Standard dosage

Hairy cell leukemia

Initial dosage

3 MIU daily for 16–24 weeks. If intolerance develops, either the daily dose must be lowered to 1.5 MIU or the schedule changed to three times weekly, or both.

Maintenance dosage

3 MIU, given three times weekly. If intolerance develops, the dose must be lowered to 1.5 MIU three times weekly.

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.

The minimum effective dose of Roferon-A in hairy cell leukemia has not been established.

Cutaneous T-cell lymphoma (CTCL)

Interferon alfa-2a (Roferon-A) produces objective tumour responses in approximately 60% of patients with CTCL. A third of these are complete responses with response duration of more than 12 months and ongoing responses after treatment discontinuation. Such tumour regression may also occur in patients who have failed to respond, or have relapsed after initially responding, to other treatment modalities. Partial responses are usually seen within 3 months, and complete responses within 6 months, although it may occasionally take more than a year to achieve the best response.

Initial dosage

Roferon-A should be given by injection and escalated to 18 MIU daily for a total of twelve weeks in patients of 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

Roferon-A should be given three times weekly at the maximum dose tolerated by the patient, but not exceeding 18 MIU.

The use of lower doses in combination with other forms of therapy (retinoids or PUVA) is still in the experimental stage.

Duration of treatment

Patients should be treated for at least 8 weeks and preferably 12 weeks before the physician decides whether to continue treatment in responding patients or to discontinue treatment in non-responding patients. Responding patients should be treated for at least 12 months in order to maximise the probability of achieving a complete and lasting 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.

AIDS-related Kaposi's sarcoma

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 (weight loss greater than 10%, fever >38 °C with no known focus of infection or night sweats) and a baseline T4-lymphocyte count of greater than 0.4×10^9/l.

Objective tumour regression (complete or partial response) has been observed in approximately 45% of patients with baseline T-lymphocyte counts greater than 0.4×10^9/l.

Responding patients experienced tumour regression and prolongation of survival time.

Response to treatment was generally evident after 3 months of therapy.

Initial dosage

Roferon-A should be given by injection and escalated if possible to at least 18 MIU daily, and ideally to 36 MIU daily, for a total of 10–12 weeks in patients of 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

Roferon-A should be given three times weekly at the maximum dose tolerated by the patient, but not exceeding 36 MIU.

Duration of treatment

The evolution of lesions should be documented to determine response to therapy. Patients should be treated for at least 10 weeks and preferably 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 20 consecutive months. If a

response to treatment occurs, treatment should continue at least until there is no further evidence of tumour. The optimal duration of Roferon-A treatment for AIDS-related Kaposi's sarcoma has not been determined.

Note

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

Advanced renal cell carcinoma

Roferon-A with vinblastine

Roferon-A should be given at a dose of 3 MIU three times weekly for one week, followed by 9 MIU three times weekly for a further week; after this a dose of 18 MIU three times weekly should be given. At the same time vinblastine should be given intravenously (i.v.) at a dose of 0.1 mg/kg once every three weeks in accordance with the manufacturer's instructions.

Should the dose of 18 MIU of Roferon-A three times weekly not be tolerated, it can be reduced to 9 MIU three times weekly.

Patients should be treated for at least 3 months and at most 12 months, or until the onset of disease progression. Patients who show a complete response to treatment can cease treatment 3 months after identification of their good response.

Roferon-A with bevacizumab

Roferon-A should be given at a dose of 9 MIU three times weekly until disease progression or for up to 12 months.
Roferon-A therapy may be initiated at a lower dose (3 or 6 MIU), although the recommended dose of 9 MIU should be reached within the first two weeks of treatment.

If the Roferon-A dosage of 9 MIU three times weekly is not tolerated, it may be reduced to a minimum dose of 3 MIU three times weekly.

The Roferon-A injections are given after completing the bevacizumab infusion. For the dosage of bevacizumab, please see the prescribing information for Avastin.

Chronic myelogenous leukemia (CML)

In patients for whom an HLA-identical donor is available, allogeneic bone-marrow transplantation should be considered.

Dosage

Roferon-A should be given to patients of 18 years or over by injection for a period of 8–12 weeks. 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 at least 8 weeks and preferably 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. Responding

patients should be treated until complete hematological remission is achieved or for a maximum of 18 months. All patients with complete hematological response should continue treatment with 9 MIU daily (optimum) or 9 MIU three times weekly (minimum) in order to achieve cytogenetic remission in the shortest possible time. The optimal duration of Roferon-A treatment for chronic myelogenous leukemia has not been determined.

Surgically resected AJCC stage II malignant melanoma

Recommended dose

Roferon-A should be given at a dose of 3 MIU three times weekly.

Duration of treatment

Patients should be treated for 18 months, starting at the latest six weeks after surgery.

Chronic hepatitis C

(The diagnosis should be made by a specialist.)

Roferon-A in combination with ribavirin

Combination therapy with ribavirin: When interferon alfa-2a is used in combination with ribavirin in patients with chronic hepatitis C, please refer also to the prescribing information for ribavirin.

Relapsed patients

Roferon-A is used in combination with ribavirin for the treatment of chronic hepatitis C in adult patients who have relapsed after responding to monotherapy with interferon alfa.

Dosage of Roferon-A

4.5 MIU three times weekly by injection for a period of 6 months.

Dosage of ribavirin

1000–1200 mg daily in two divided doses (one in the morning with breakfast and one with the evening meal). For further information and details on the dosage and method of administration of ribavirin, please refer to the prescribing information for ribavirin.

Treatment of previously untreated (naive) patients

The efficacy of interferon alfa-2a in the treatment of hepatitis C is increased by combination with ribavirin. Roferon-A should be used as monotherapy only in case of intolerance or contraindications to ribavirin.

Dosage of Roferon-A

3–4.5 MIU three times weekly by injection for a period of at least 6 months. Treatment should be continued for at least 6 more months in patients with a high pretreatment viral load of genotype 1 who are HCV RNA-negative after 6 months.

Dosage of ribavirin

See above.

Other negative prognostic factors (age >40 years, male sex, bridging fibrosis) should be taken into account when deciding whether to extend therapy to 12 months.

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

Roferon-A monotherapy

Roferon-A should be used as monotherapy only in case of intolerance or contraindications to ribavirin.

Dosage recommendation

6 MIU three times weekly (e.g. Monday, Wednesday and Friday) for 3 months.

Patients whose transaminase levels have normalised after 8 weeks receive the initial dose of 6 MIU three times weekly for an additional 1 month (total of 3 months), followed by 9 months' therapy with a maintenance dose of 3 MIU three times weekly.

Duration of treatment

The duration of treatment should be restricted to 12 months.

Discontinuation of treatment

Treatment should be discontinued in patients whose transaminase levels have not normalised at 8 weeks.

Relapse

In patients who relapse (generally 3 months after the end of treatment), the value of repeated therapy with a higher dose has not been established.

Chronic active hepatitis B

Dosage recommendations

The recommended dose is between 5 and 10 MIU three times weekly (e.g. Monday, Wednesday, Friday) for a maximum of 4 months. If the genomic markers of viral replication or HBe antigen in the serum have not decreased after 2 months of therapy (>50% reduction compared to baseline), treatment should be discontinued. The appearance of anti-HBe antibody concurrently with a reduction in genomic markers of viral replication is indicative of a good early response to treatment.

Special dosage instructions

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 advisable to resume treatment at a lower dosage. The efficacy of such reduced dosages has not been established.

Dosage should be modified to take into account the constitutional symptoms, myelosuppressive effects and other clinical or laboratory test abnormalities caused by Roferon-A and concurrently administered medicines or the effects of previous radiotherapy 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.

Children

Children with chronic active hepatitis B can be given up to 10 MIU/m^2 three times weekly. However, the efficacy of therapy has not been established.

Roferon-A should not be used in children for other indications.

Warning

Because of its content of benzyl alcohol, Roferon-A should not be used in newborn infants, especially if premature, or in children under 3 years of age (see *Contraindications*). In rare cases, benzyl alcohol may lead to life-threatening conditions and anaphylactoid reactions in children under 3 years of age. Roferon-A should therefore not be used in newborn infants or children under 3 years of age. Roferon-A solution contains 10 mg/ml benzyl alcohol.

Contraindications

Hypersensitivity to the active substance, to other interferon preparations, to mouse immunoglobulin, or to any of the constituent excipients.

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.

Existing serious heart disease or a history of any kind of heart disease.

Severe renal or hepatic failure or severe bone marrow dysfunction.

Epilepsy and/or other disorders of central nervous system function.

Chronic hepatitis with advanced decompensated cirrhosis of the liver.

Chronic hepatitis in patients who are being or have recently been treated with immunosuppressive agents, excluding prior short-term treatment with steroids.

Autoimmune chronic hepatitis (cases of exacerbation on treatment with interferon alfa have been described).

Roferon-A must not be used in combination with ribavirin in pregnant women. Please refer also to the prescribing information for ribavirin.

Warnings and Precautions

Roferon-A should be administered under the supervision of a physician experienced in the use of anticancer or antiviral drugs or of a hepatitis specialist. Appropriate management of the 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 adverse reactions may occur.

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

Infections

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other possible causes of persistent fever must be ruled out, especially 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 interferon therapy should be considered.

Heart disease

Roferon-A should not be administered to patients with existing or previous heart disease. Although no direct cardiotoxic effect has been demonstrated, it is likely that acute adverse effects (e.g. fever, chills) frequently associated with administration of Roferon-A may exacerbate pre-existing cardiac conditions.

Central nervous system disorders

Roferon-A should not be administered to patients with epileptic disorders and/or other disorders of central nervous system function. Regular neurological examination of all patients is recommended.

Psychiatric effects

Severe psychiatric adverse reactions can occur in patients receiving therapy with interferons, including Roferon-A. Depression, suicidal ideation and suicide attempts have been observed in patients with and without previous psychiatric illness.

Physicians should monitor all patients for evidence of depression. Caution is required in patients with a history of depression. Before starting treatment, physicians should inform patients about the possible development of depression and instruct them to report any symptoms of depression immediately. Psychiatric intervention and/or drug discontinuation should be considered in such cases.

Bone marrow suppression

Particular caution is required when Roferon-A is administered to patients with severe myelosuppression, as it has a suppressive effect on the bone marrow, leading to a fall in the white blood count (particularly granulocytes), platelet count and, less commonly, hemoglobin concentration. This can lead to an increased risk of infection or of bleeding. Patients should be closely monitored for such changes. Blood counts should be performed both before and at appropriate intervals during Roferon-A therapy.

Hepatic function

Caution is required 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.

In rare cases, severe hepatic dysfunction and liver failure have been reported after treatment with interferon alfa.

Roferon-A has been found to be ineffective in patients with chronic active hepatitis B who are co-infected with human immunodeficiency virus (HIV).

Ophthalmological effects

As with other interferons, retinopathy including retinal hemorrhages, cotton wool spots, papilledema, retinal artery or vein occlusion and optic neuropathy, which may result in loss of vision, have been reported after treatment with Roferon-A. Any patient complaining of decreased or lost 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 must be discontinued in patients who develop new or worsening ophthalmological disorders.

Hypersensitivity

If a hypersensitivity reaction (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) occurs during treatment with Roferon-A, either alone or in combination with ribavirin, treatment must be discontinued and appropriate medical therapy instituted immediately. Transient rashes do not necessitate interruption of treatment.

Endocrinological effects

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 disease

The development of various autoantibodies has been reported during treatment with alfa interferons. Clinical manifestations of autoimmune disease during interferon therapy occur more commonly in subjects predisposed to the development of autoimmune disorders.

Autoimmune phenomena such as vasculitis, rheumatoid arthritis, hemolytic anemia, thyroid dysfunction and systemic lupus erythematosus have been observed rarely in patients receiving Roferon-A. In patients with a predisposition to or a clinical history of autoimmune disorders, monitoring of symptoms suggestive of these disorders and measurement of autoantibodies and TSH level are recommended.

Use of Roferon-A 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 alfa interferons, graft rejections have been reported in patients taking Roferon-A.

Combination therapy with ribavirin

When interferon alfa-2a is used in combination with ribavirin in patients with chronic hepatitis C, please refer also to the prescribing information for ribavirin.

Children

Children with chronic active hepatitis B can be given up to 10 MIU/m^2 three times weekly. However, the efficacy of therapy has not been established.

Roferon-A should not be used in children for other indications.

Treatment with Roferon-A may be prescribed and initiated only by experienced physicians.

Interactions

Alfa interferons can affect the oxidative metabolic process by reducing the activity of hepatic microsomal cytochrome enzymes of the P450 group. Although the clinical relevance is still unclear, this should be taken into account when prescribing concomitant therapy with drugs metabolised by this route. Reduced clearance of theophylline has been reported following concomitant administration of alfa interferons.

Interferons have been observed to increase the neurotoxic, hematotoxic and cardiotoxic effects of previously or concurrently administered drugs. Interactions could occur following concurrent administration of drugs that act on the central nervous system.

Combination therapy with ribavirin

When interferon alfa-2a is used in combination with ribavirin in patients with chronic hepatitis C, please refer also to the prescribing information for ribavirin.

Combination therapy with bevacizumab

Bevacizumab does not affect the pharmacokinetics of interferon alfa-2a.

Pregnancy and Lactation

Men and women should practice effective contraception during treatment with Roferon-A.

No clinical data are available on use in pregnant women.

No adequate animal studies are available on the effect on pregnancy and embryonic, fetal and/or postnatal development. The potential risk is unknown.

As with the use of anticancer drugs in general, effective contraception should be practised.

Although animal tests do not indicate that Roferon-A is a teratogen, harm to the fetus from use during pregnancy cannot be excluded. Roferon-A should therefore not be used unless it is clearly required. An abortifacient effect was observed when grossly excessive doses were administered to rhesus monkeys in early to mid-gestation.

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

The excipient benzyl alcohol can cross the placenta. The possibility of toxicity should be borne in mind in premature infants whose mothers have received Roferon-A solution for injection immediately prior to birth or Cesarean section.

The combination of Roferon-A and ribavirin must not be used in pregnant women.

Women of reproductive age and their partners should not receive the combination of Roferon-A and ribavirin unless the patient and his/her partner are taking effective contraceptive measures.

Combination therapy with ribavirin: When interferon alfa-2a is used in combination with ribavirin in patients with chronic hepatitis C, please refer also to the prescribing information for ribavirin.

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.

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 that were often at an advanced stage and refractory to previous treatment, patients with chronic hepatitis B and patients with chronic hepatitis C. In each case the frequency of adverse reactions was higher in cancer patients than in hepatitis patients.

About two-thirds of cancer patients in clinical studies experienced anorexia and one-half nausea. Cardiovascular and respiratory disorders such as transient hypotension, hypertension, edema, cyanosis, arrhythmias, palpitations and chest pain were seen in about one-fifth of cancer patients. Most cancer patients received doses significantly higher than that currently recommended for chronic hepatitis B and C, which probably explains the greater frequency and severity of adverse reactions in this patient group compared to patients with hepatitis B and C, in whom adverse reactions are usually transient and who generally return to pretreatment status one to two weeks after the end of therapy; increased hair loss may persist for several weeks. Cardiovascular reactions were less common in hepatitis B and C patients.

General symptoms

A quarter to two-thirds of patients in clinical studies experienced flu-like symptoms such as fatigue, fever, chills, appetite loss, myalgia, headache, arthralgia and diaphoresis. These flu-like symptoms can often be alleviated by paracetamol and tend to diminish with continued therapy or dose modification, although continued therapy can lead to lethargy, weakness and fatigue.

Infections and infestations

Rare: pneumonia, *Herpes simplex* (including exacerbations of *herpes labialis*)

Blood and lymphatic system

Very common: leukopenia

Common: thrombocytopenia, anemia

Rare: agranulocytosis, hemolytic anemia

Very rare: idiopathic thrombocytopenic purpura

In myelosuppressed patients, thrombocytopenia and decreased hemoglobin occur more frequently. Recovery of severe hematological deviations to pretreatment levels usually occurred within seven to ten days after discontinuation of Roferon-A treatment.

Immune system

Rare: autoimmune diseases, acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchospasm, anaphylactic reaction)

Very rare: sarcoidosis

Endocrine disorders

Rare: hyperthyroidism, hypothyroidism, thyroid dysfunction

Metabolic and nutritional disorders

Very common: appetite loss, nausea, hypocalcemia

Uncommon: electrolyte disturbance, dehydration

Rare: hyperglycemia

Very rare: diabetes mellitus, hypertriglyceridemia/hyperlipidemia

Psychiatric disorders

Uncommon: depression, anxiety, mental state changes, confusion, abnormal behaviour, nervousness, impaired memory, sleep disturbances

Rare: suicide, attempted suicide, suicidal ideation

Nervous system

Very common: headache

Uncommon: neuropathy, dizziness, somnolence, taste disturbance, paresthesia, hypoesthesia, tremor

Rare: coma, stroke, convulsions, transient erectile dysfunction

Eyes

Uncommon: conjunctivitis, visual disturbance

Rare: ischemic retinopathy

Very rare: optic neuropathy, central retinal artery occlusion, central retinal vein thrombosis, retinopathy, retinal hemorrhage, papilledema, retinal exudation

Ear and inner ear

Uncommon: vertigo

Heart

Uncommon: cardiac arrhythmias, including atrioventricular block, palpitations

Rare: cardiorespiratory arrest, myocardial infarction, decompensated heart failure, pulmonary edema, cyanosis

Vascular system

Uncommon: hypertension, hypotension

Rare: vasculitis

Respiratory organs

Rare: dyspnea, cough

Gastrointestinal disorders

Very common: diarrhea

Common: nausea/vomiting

Uncommon: abdominal pain, dry mouth

Rare: intestinal hypermotility, constipation, dyspepsia, flatulence, pancreatitis
Very rare: reactivation of gastric ulcer, non-life-threatening gastrointestinal bleeding

Hepatobiliary system
Rare: hepatic failure, hepatitis, hepatic impairment

Skin and subcutaneous tissue disorders
Very common: hair loss (reversible after discontinuation of the drug; increased hair loss may persist for several weeks after the end of treatment), increased sweating
Uncommon: exacerbation or provocation of psoriasis, pruritus
Rare: rash, dry skin, epistaxis, dry mucous membranes, rhinorrhea

Musculoskeletal system
Very common: myalgia, arthralgia
Rare: systemic lupus erythematosus, arthritis

Kidneys and urinary tract
Uncommon: proteinuria and increased cell count in urine
Rare: acute renal failure (mostly in cancer patients with renal disease), renal impairment

General symptoms and administration site reactions
Very common: flu-like illness, fatigue, fever, chills, appetite loss
Uncommon: thoracic pain, edema
Very rare: injection site necrosis, injection site reactions

Laboratory tests
Uncommon: elevated blood levels of ALT, alkaline phosphatase and transaminases, weight loss
Rare: elevated blood levels of LDH, bilirubin, creatinine, uric acid and urea

Neutralising antibodies
Anti-interferon antibodies: Neutralising antibodies to proteins may be formed in some patients 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.

Data from clinical trials in which Roferon-A was used indicate that neutralising antibodies to Roferon-A developed in approximately one-fifth of patients. In responding hepatitis C patients in whom neutralising antibodies developed, it was observed that the effect of the medication tended to wane with continued treatment, whereas in patients who did not form such antibodies the response to treatment was more prolonged. No information is available on other clinical effects of antibodies to Roferon-A. The clinical relevance of the formation of these antibodies is not fully understood.

Combination therapy with ribavirin

When interferon alfa-2a is used in combination with ribavirin in patients with chronic hepatitis C, please refer also to the prescribing information for ribavirin.

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

Postmarketing experience

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

Overdosage

There are no reports of overdosage, but repeated very 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 usually recover within days after discontinuation of therapy, given appropriate supportive care. Coma was observed in 0.4% of cancer patients in clinical trials.

Properties and Effects

ATC code: L03AB04

Mechanism of action/Pharmacodynamics

Interferon alfa-2a is a highly purified protein containing 165 amino acids with an approximate molecular weight of 19,000 daltons. It is produced by recombinant DNA technology using a genetically engineered *E. coli* strain whose DNA codes for this human protein.

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 mechanism responsible for the antitumour action of Roferon-A is not yet known. However, 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. The degree of antiproliferative activity is variable.

The antitumour effects of Roferon-A have been demonstrated in patients with hairy cell leukemia, cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome), AIDS-related Kaposi's sarcoma and chronic myelogenous leukemia.

Adjuvant therapy with a low dose of Roferon-A prolongs disease-free interval in patients with no clinically detectable nodal or distant metastases after resection of a melanoma (tumour thickness >1.5 mm).

The antiviral effects of Roferon-A have been documented in patients with chronic active hepatitis B and chronic hepatitis C.

Clinical efficacy

Chronic hepatitis C

The therapeutic efficacy of interferon alfa-2a alone and in combination with ribavirin (24 weeks of treatment in each case) was compared in a double-blind randomised clinical trial in relapsed patients with virologically, biochemically and histologically documented chronic hepatitis C (n=49 Roferon-A and ribavirin; n=50 Roferon-A and placebo). Six months after the end of treatment sustained biochemical and virological response and histological improvement were assessed.

A statistically significant increase in sustained virological and biochemical response (ALT and HCV-RNA) was observed in relapsed patients given interferon alfa plus ribavirin versus those given interferon alfa monotherapy (43% versus 4%; $p<0.01$). The favourable profile of the combination therapy was also reflected in the response rates relative to HCV genotype or baseline viral load. Although the sustained response rates in patients with HCV genotype 1 were lower than in the overall population (30% versus 0% in the monotherapy arm), the relative benefit of ribavirin in combination with interferon alfa-2a is particularly significant in this group of patients. In addition, the histological improvement favoured the combination therapy.

Supportive favourable results from a small study in naive patients were reported using interferon alfa-2a (3 MIU three times weekly) with ribavirin.

For further information on pharmacodynamic properties, please refer to the prescribing information for ribavirin.

Advanced renal cell carcinoma

Treatment with Roferon-A in combination with vinblastine leads to a global response rate of approximately 20%, delays disease progression and prolongs overall survival time in patients with advanced renal cell carcinoma.

Roferon-A in combination with bevacizumab as first-line treatment in patients with advanced and/or metastatic renal cell carcinoma showed prolongation of progression-free survival (median 10.2 vs 5.4 months; hazard ratio 0.63; $p<0.0001$) and an increased response rate (31% vs 13%; $p<0.0001$) compared to Roferon-A monotherapy.

However, the observed 2-month prolongation of overall survival was not significant (median 23.3 vs 21.3 months; hazard ratio 0.91; $p=0.3360$). A retrospective subgroup analysis of this study involving 131 patients showed that reduction of the IFN alfa-2a dose from 9 MIU to either 6 or 3 MIU three times weekly, as permitted in the protocol, did not appear to reduce the efficacy of Avastin/IFN combination therapy. (Progression-free survival after 6, 12 and 18 months: 73, 52 and 21% in the “reduced IFN” population vs 61, 43 and 17% in the total population).

For further information on combination with bevacizumab, please see the prescribing information for Avastin.

Pharmacokinetics

Absorption

After intramuscular (i.m.) injection, the absolute bioavailability is greater than 80%. After i.m. and s.c. administration of 36 MIU, peak serum concentrations ranged from 1500 to 2580 pg/ml (mean: 2020 pg/ml) at a mean time to peak of 3.8 hours, and from 1250 to 2320 pg/ml (mean: 1730 pg/ml) at a mean time to peak of 7.3 hours, respectively.

Distribution

After i.v. infusion of 36 MIU in healthy subjects, the steady-state distribution volume ranged from 0.223 to 0.748 l/kg (mean: 0.400 l/kg). Dose-proportional increases in serum concentrations were observed after single doses up to 198 MIU.

The serum concentrations of interferon alfa-2a showed considerable intersubject variation in both healthy volunteers and patients with disseminated cancer.

Metabolism

Alfa interferons undergo rapid proteolytic degradation during tubular reabsorption and – to a lesser extent – in the liver.

Elimination

Renal catabolism is the major pathway for alfa interferon elimination. Liver metabolism and subsequent biliary excretion are considered minor pathways of elimination for alfa interferons. In healthy subjects, interferon alfa-2a exhibited 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/kg/min (mean: 2.79 ml/kg/min) after an i.v. infusion of 36 MIU (2.2×10^8 pg).

Pharmacokinetics in Special Patient Groups

The pharmacokinetics of interferon alfa-2a after single i.m. doses to patients with disseminated cancer, chronic hepatitis C and chronic active hepatitis B were similar to those found in healthy volunteers.

In some individuals, repeated i.m. administration of interferon alfa-2a resulted in serum levels two to four times greater than those seen after single doses.

There were no changes in the distribution or elimination of interferon alfa-2a during twice-daily (0.5–36 MIU), once-daily (1–54 MIU), or three-times-weekly (1–136 MIU) dosing regimens lasting up to 28 days.

For further information on pharmacokinetic properties, please refer to the prescribing information for ribavirin.

Preclinical Data

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

Because of the species specificity of human interferon, Roferon-A has been subjected to only limited toxicity testing. The acute toxicity of Roferon-A has been studied in mice, rats, rabbits and ferrets at doses up to 30 MIU/kg i.v. and 500 MIU/kg i.m. No treatment-related mortality was noted in any species studied given Roferon-A by either route of administration. With grossly excessive doses, no significant adverse effects were observed except for an abortifacient effect when administered to rhesus monkeys in early to mid-gestation and transient menstrual cycle irregularities, including prolonged menstrual periods, in non-pregnant monkeys.

Mutagenesis: Mutagenic effects of Roferon-A have not been observed experimentally.

For additional preclinical safety data on combination therapy with ribavirin in patients with hepatitis C, please refer to the prescribing information for ribavirin.

Additional Information

Stability

Prefilled syringes and cartridges

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Roferon-A cartridges should be used within one month of first withdrawal of the product.

Special precautions for storage

Prefilled syringes and cartridges

Store in the original pack to protect the contents from light. Store in a refrigerator (2–8 °C). Do not freeze.

Cartridges

Cartridges that have been inserted into the Roferon-Pen or are kept in the case provided have a shelf life of up to one month at temperatures not exceeding 25 °C. However, where possible the cartridges should be kept in a refrigerator and returned there after each injection. Under no circumstances should the pen or the case be frozen if it contains a cartridge.

Instructions for use and handling

The cartridges are designed for s.c. injection using the Roferon-Pen. Roferon-A cartridges are for multidose and single-patient use only and should be used exclusively with the Roferon-Pen. PenFine® needles are recommended for use with the pen and cartridges, though certain other types of needle can also be used. A new sterile needle must be used for each injection. Roferon-A cartridges should be used within one month of first withdrawal of the product. After each injection the Roferon-Pen/cartridge combination should be returned to the refrigerator to protect the contents from light. Once opened, however, the Roferon-Pen/cartridge combination can be stored protected from light at up to 25 °C for a maximum of one month. The date of first use of a cartridge should be noted on the label supplied with the cartridge, and this label should be affixed to the box containing the Roferon-Pen. Detailed instructions for use of the Roferon-Pen are provided in the package containing the Pen.

Any medicinal product remaining unused after the end of treatment or by the expiry date should be properly disposed of.

Packs

Roferon-A 3 MIU/0.5 ml prefilled syringes containing solution for injection	1
Roferon-A 4.5 MIU/0.5 ml prefilled syringes containing solution for injection	1
Roferon-A 6 MIU/0.5 ml prefilled syringes containing solution for injection	1
Roferon-A 9 MIU/0.5 ml prefilled syringes containing solution for injection	1
Roferon-A 18 MIU/0.6 ml cartridges containing solution for injection	1

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at February 2012

Prefilled syringes:
Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel

Cartridges:
Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland, by Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany