

Data Sheet

Roferon[®]-A

Interferon alfa-2a 3, 6 and 9 MIU solution for injection

Antiviral and antineoplastic agent

Pharmaceutical Form

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

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 pre-filled syringe (for single-dose, subcutaneous (sc) injection) contains 3, 6 or 9 MIU (million international units) interferon alfa-2a in 0.5 mL.

Excipients

Ammonium acetate, sodium chloride, benzyl alcohol 1% (as a preservative), polysorbate 80 with buffers of glacial acetic acid, sodium hydroxide to pH5.0 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.

Clinical Particulars

Therapeutic Indications

Roferon-A is indicated for the treatment of basal cell carcinoma, carcinoid syndrome, chronic active hepatitis B, chronic lymphocytic leukaemia (early stage), chronic myelogenous leukaemia, chronic non-A, non-B hepatitis (hepatitis C), condylomata acuminata, cutaneous T cell lymphoma (mycosis fungoides and Sezary syndrome), essential thrombocythaemia, hairy cell leukaemia, Kaposi's sarcoma associated with AIDS, malignant melanoma, multiple myeloma, non-Hodgkin's lymphoma (low and intermediate grade), renal cell carcinoma (recurrent, advanced and/or metastatic).

Dosage and Administration

Roferon-A is usually administered as a subcutaneous (sc) injection. Each pre-filled syringe pack includes a 12 mm needle for sc injection.

Roferon-A may be administered by intramuscular (im) injection into either the deltoid or gluteus muscle. The appropriate needle will need to be used.

See Special Remarks – Instructions for use, handling and disposal.

Basal Cell Carcinoma

The recommended dosage, depending on the size of the lesion, is 1.5 – 6 MIU of Roferon-A three times a week, administered intralesionally or sc for 3 weeks.

It may take up to 8 weeks for the treatment effect to become apparent.

Carcinoid Syndrome

The recommended dosage is 3 – 6 MIU three times a week by injection.

Chronic Active Hepatitis B

Therapeutic trials in patients with chronic active hepatitis B show that Roferon-A therapy at doses equivalent to ≥ 2.5 MIU/m² three times weekly for four to six months is associated with inhibition of viral replication, development of a specific humoral immune response and a reduction or disappearance of necroinflammatory disease of the liver. Response to therapy is often signalled by a transient asymptomatic acute hepatitis 'flare' with a serum transaminase peak accompanied by a fall in the level of genomic and antigenic (especially HB_e) markers of viral replication.

Loss or reduction of HB_s antigenaemia usually occurs over a period of many months. The appearance of anti-HB_e and in some patients anti-HB_s antibody in the serum signals antiviral immunity. Maximal response to therapy often occurs weeks or months after the end of treatment. Patients with active disease respond better to therapy than those with hypoactive disease as defined by liver biopsy and/or serum alanine aminotransferase (ALAT) levels. Patients with ALAT levels of greater than eight times the upper limit of the normal range have more than double the chance of responding to Roferon-A therapy than those with normal or moderately elevated serum ALAT levels.

Doses ≤ 1.5 MIU three times for 16 weeks are suboptimally effective. Some patients require doses up to the equivalent of 10 MIU/M² for three to six months to benefit from therapy.

Dosage recommendations: The optimal schedule of treatment has not yet been established. The dose is usually in the range of 2.5 MIU to 5.0 MIU /m² body surface administered by injection three times per week for a period of 4 – 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 medication.

If no improvement has been observed after 3 – 4 months of treatment, discontinuation of therapy should be considered.

Chronic Lymphocytic Leukaemia

A typical monotherapy induction regimen for Roferon-A in early stage chronic lymphocytic leukaemia would be to give up to 6 MIU by injection per day. A typical combination regimen would include alfa-interferon at a dose of up to 6 MIU by injection three times per week. Induction or co-induction therapy should be given for 3 months, followed by a further 12 months in responding patients. For maintenance therapy a dose of 3 MIU by injection three times per week would be appropriate. Individual patient response and tolerability is highly variable and is affected by such factors as the grade of the disease at induction of alfa-interferon therapy, patient age, other chemotherapy, etc. It is recommended that maintenance therapy be given until relapse. Published clinical trials indicate that Roferon-A maintenance therapy has been given following other chemotherapy regimens for periods up to 18 months.

Chronic Myelogenous Leukaemia (CML)

Initial dosage: The optimal induction dose is 9 MIU daily for at least 6 months. This is usually achieved after a gradual dose increase (e.g. 3 MIU daily for the first week, 6 MIU daily the second week and 9 MIU daily after that).

Maintenance dosage: Start at 9 MIU three times a week. The dose can be adjusted, according to WBC counts, cytogenetic response and side effects.

Duration of treatment: Maintenance treatment should continue for another 12 – 24 months.

Chronic Non-A, Non-B Hepatitis (Hepatitis C)

Roferon-A is indicated for the treatment of adult patients with chronic hepatitis C who are positive for HCV antibodies or HCV RNA 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 in case of intolerance or contraindication to ribavirin.

Roferon-A monotherapy

Initial dosage: Roferon-A should be administered at a dose of 6 MIU by sc or im injection three times a week for 3 months as induction therapy.

Maintenance dosage: Patients whose serum ALT has normalised 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 normalised should stop treatment.

Note: The majority of patients who relapse after adequate treatment with Roferon-A alone do so within 4 months of ending treatment.

Roferon-A in combination with ribavirin

Relapsed Patients

Roferon-A is given in combination with ribavirin 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 should be given at a dosage of 4.5 MIU 3 times per week by sc or im injection for a period of 6 months.

Dosage of ribavirin: Ribavirin should be given at a dosage of 1000 mg to 1200 mg/day in two divided doses (once in the morning with breakfast and once with the evening meal).

For more information on the combination use with ribavirin, refer to the prescribing information for ribavirin.

Treatment-Naïve Patients

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

Dosage: Roferon-A should be given by injection at a dosage of 3 – 4.5 MIU 3 times per week 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 pre-treatment viral load.

Dosage of ribavirin: See above. 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 not generally become sustained virologic responders (HCV-RNA below lower limit of detection 6 months after withdrawal of treatment).

Condylomata Acuminata (Genital Warts)

A total daily dose of 3 MIU should be given either as one sc injection or divided into 1 – 5 intralesional injections. The dose may be reduced if side effects are not tolerated, but 1 MIU is the minimum effective dose. Roferon-A should be administered three times a week for a least 3 weeks. If intralesional injections are to be given, the lesions should first be cleaned with a sterile alcohol pad. The injections should be made at the base of the lesion using a fine (30 gauge) needle.

Cutaneous T Cell Lymphoma (CTCL)

Roferon-A produces objective tumour responses in approximately 60% of patients with CTCL. About one third of these responses are complete responses with response duration of more than 12 months and ongoing responses after treatment discontinuation. These tumour regressions can also be achieved in patients who failed to respond or relapsed after having responded 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 1 year to reach the best response.

Initial dosage: Roferon-A should be given by injection, and escalated to 18 MIU daily for a total of 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 – 70	18 MIU daily

Maintenance dosage: Roferon-A should be given by injection three times per week at the maximum dose which is acceptable to the patient, but not exceeding 18 MIU.

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. Minimum treatment duration in responding patients should be 12 months in order to maximise the chance to achieve a complete response and improve the chance for a 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.

Essential Thrombocythaemia

Thrombocytosis is a frequent concomitant phenomenon in chronic myelogenous leukaemia (CML) and is the hallmark of essential thrombocythaemia. The morbid nature of severe thrombocytosis is reflected by the frequent manifestation of a serious thrombotic or haemorrhagic diathesis. Interferon alfa-2a has been clearly shown to cause a decrease in excessive platelet counts within a few days, to reduce the frequency of thrombocytosis associated with thrombo-haemorrhagic complications and to have no leukaemogenic potential. Therefore, a non-leukaemogenic therapy is recommended with interferon alfa-2a for the treatment of patients with excessive thrombocytosis in CML, even in the absence of a cytogenetic response, and in other myeloproliferative disorders. The recommended dosage for thrombocytosis in CML is the same as that recommended above for the treatment of CML.

The recommended dosage for thrombocytosis in myeloproliferative diseases other than CML is:

Days 1 – 3	3 MIU daily
Days 4 – 30	6 MIU daily

A well-tolerated maintenance dose of 1 – 3 MIU daily, two to three times a week, is usually enough to maintain platelet counts within the normal range. The dose however, needs to be titrated individually for each patient to his/her highest tolerated dose.

Hairy Cell Leukaemia

Initial dosage: Roferon-A should be given by injection at a dose of 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: Roferon-A should be given by injection at a dose of 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 nonresponding patients. Patients have been treated for up to 20 consecutive months. The optimal duration of Roferon-A treatment for hairy cell leukaemia has not been determined.

Note: Subcutaneous administration is recommended for thrombocytopenic patients (platelet count less than $50 \times 10^9/L$) or patients at risk of bleeding.

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

Kaposi's Sarcoma Associated With AIDS

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 bodyweight, fever $> 38^\circ C$

with no identified source of infection or night sweats) and a baseline T4 lymphocyte count of greater than 400 cells/mm³.

Objective tumour regression (complete and partial responses) has been observed in approximately 45% of patients with baseline T4 lymphocyte counts of greater than 400 cells/mm³.

Responding patients experienced tumour regression and prolongation of survival.

Patients generally showed evidence of response after approximately 3 months of therapy.

Initial dosage: Roferon-A should be given by injection, and escalated to at least 18 MIU daily and if possible 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 – 70	36 MIU daily

Maintenance dosage: Roferon-A should be given by injection three times per week at the maximum dose which is acceptable to 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 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 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 3 MIU of Roferon-A given daily showed a lower response rate than those treated with the recommended dosage.

Malignant Melanoma

Between 10% and 25% of patients with advanced malignant melanoma showed objective regression of cutaneous and visceral tumours on Roferon-A therapy. Lower response rates were observed using doses of less than 18 MIU three times a week. Responding patients survived longer than nonresponding patients.

Roferon-A monotherapy

Initial dosage: Roferon-A should be given by injection at a dosage of 18 MIU three times a week for a total of 8 – 12 weeks.

Maintenance dosage: Roferon-A should be given by injection at a dosage of 18 MIU three times a week or at the maximum dose which is acceptable to the patient.

Duration of treatment: Patients should be treated for a minimum of 8 weeks and preferably for 12 weeks before the physician decides to continue treatment in responding patients or to discontinue

treatment in nonresponding patients. Patients have been treated for up to 24 consecutive months. The optimal duration of treatment for advanced malignant melanoma has not been determined.

Roferon-A with dacarbazine (DTIC)

9 – 18 MIU of Roferon-A should be given daily or three times a week by injection. Concomitant treatment with dacarbazine should be given as a single iv infusion at 21 day intervals, starting at 200mg/m² with dose increments up to 400 and 800mg/m² if tolerated.

Multiple Myeloma

A typical monotherapy induction regimen would be an escalating dosage to 18 MIU per day or the maximum tolerated dose if below 18 MIU per day. A typical combination regimen would include interferon at a daily dose of 3 – 6 MIU per day. For maintenance therapy a dose of 3 MIU/m² three times per week has been shown to be effective. Individual patient tolerance is highly variable and is affected by such factors as performance status, patient age, other chemotherapy, etc.

Non-Hodgkin's Lymphoma

A typical monotherapy induction regimen for Roferon-A in low and intermediate grades would be to give up to 6 MIU by injection per day. A typical combination regimen would include alfa-interferon at a dose of up to 6 MIU by injection three times per week. For maintenance therapy a dose of 3 MIU by injection three times per week would be appropriate. Individual patient response and tolerability is highly variable and is affected by such factors as the grade of the disease at induction of alfa-interferon therapy, patient age, other chemotherapy, etc.

Renal Cell Carcinoma (RCC)

Highest tumour response rates have been observed in patients with recurrent or metastatic carcinoma 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, compared to moderate dose Roferon-A monotherapy given three times per week. Patients treated with low-dose Roferon-A (2 MIU/m² body surface area given daily) did not show response to treatment. The combination of Roferon-A with vinblastine only results in small increases in the frequency of mild to moderate leukopenia and granulocytopenia compared with monotherapy. The duration of disease response and duration of survival are similar in patients who respond to either Roferon-A monotherapy or Roferon-A with vinblastine combination therapy.

Roferon-A monotherapy

Initial dosage: Roferon-A should be given by injection, and 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 – 70 : 36 MIU daily

Maintenance dosage: Roferon-A should be given by injection three times per week at the maximum dose which is acceptable to the patient, but not exceeding 36 MIU.

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.

Roferon-A with vinblastine

Initial dosage: 18 MIU of Roferon-A should be given by injection three times per week for a total of 8 – 12 weeks. Efforts should be made to maintain that dose; however, if it is not tolerable, the maximum dose which is acceptable to the patient should be used. During this period, concurrent vinblastine should be given by intravenous injection according to the manufacturer's instructions at a dosage of 0.1 mg/kg bodyweight, once every 3 weeks.

Maintenance dosage: 18 MIU of Roferon-A should be given by injection three times per week or, if not tolerable, the maximum dose which is acceptable to the patient. The dose should not exceed 18 MIU. During maintenance, concurrent vinblastine should be given by intravenous injection according to the manufacturer's instructions at a dosage of 0.1 mg/kg, once every 3 weeks.

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 nonresponding patients. Patients have been treated for up to 17 consecutive months. The optimal duration of combination Roferon-A and vinblastine treatment for advanced renal cell carcinoma has not been determined.

See Pharmacological Properties and Effects – Clinical/efficacy studies.

Roferon-A with Avastin® (bevacizumab)

Initial dosage: 9 MIU of Roferon-A should be given by injection three times per week until disease progression or for up to 12 months. Roferon-A therapy may be initiated with a lower dose (3 or 6 MIU). However, the recommended dose of 9 MIU should be reached within the first 2 weeks of treatment. Roferon-A injections are given after completion of the Avastin infusion, which is given according to the manufacturer's instructions.

Maintenance dosage: 9 MIU of Roferon-A should be given by injection three times per week or, if not tolerable the dosage may be reduced to a minimum dosage of 3 MIU three times per week. During maintenance, Roferon-A injections are given after completion of the Avastin infusion, which is given according to the manufacturer's instructions

Duration of treatment: Patients should be treated until disease progression or for up to 12 months.

See Pharmacological Properties and Effects – Clinical/efficacy studies.

For more information on the combination use with Avastin, refer to the Avastin Data Sheet.

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 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.

Use in Children

The use of Roferon-A in children is not recommended as the safety and effectiveness of Roferon-A in children have not been established. 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 is contraindicated in

- patients with a history of hypersensitivity to recombinant interferon alfa-2a or any component of the preparation.
- 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'.
- 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.

Warnings and Precautions

General: 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.

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

Interactions with other Medicinal 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 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.

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

Results from a controlled clinical study demonstrated no significant effect of bevacizumab on the pharmacokinetics of interferon alfa-2a.

Use in Special Populations

Pregnancy

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 foetus. Although animal tests do not indicate that Roferon-A is a teratogen, harm to the foetus 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-foetal period, an abortifacient effect was observed.

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.

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 prescribing information if interferon alfa-2a is to be administered in combination with ribavirin in patients with chronic hepatitis C.

Nursing mothers

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

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 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 ribavirin 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, diarrhoea 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, 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: Paraesthesia, 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, oedema, cyanosis, arrhythmias, palpitations and chest pain.

Rare: Coughing, mild dyspnoea, pulmonary oedema, 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, rhinorrhoea and epistaxis.

Renal and urinary system

Rare: Decreased renal function; acute renal failure, mainly in cancer patients with renal disease and/or nephrotoxic co-medications 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.

Haematopoietic system

Common: Transient leucopenia rarely requiring restriction of dosage, in myelosuppressed patients, thrombocytopenia and decreased haemoglobin.

Uncommon: In non-myelosuppressed patients, thrombocytopenia.

Rare: Decrease of haemoglobin and haematocrit. Recovery of severe haematological deviations to pre-treatment levels usually occurred within 7-10 days after discontinuing Roferon-A treatment.

Very rare: Idiopathic thrombocytopenic purpura (ITP).

Other

Rare: Hyperglycaemia, diabetes mellitus, injection site reactions including, very rarely, necrotic site reactions, autoimmune phenomena, i.e. vasculitis, arthritis, haemolytic anaemia, thyroid dysfunction and lupus erythematosus syndrome.

Very rare: Asymptomatic hypocalcaemia, sarcoidosis, hypertriglyceridaemia/hyperlipidaemia.

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 ribavirin prescribing information if interferon alfa-2a is to be administered in combination with ribavirin in 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 anaemia has been reported.

Post-marketing experience

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

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.

Pharmacological Properties and Effects

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.

Clinical/efficacy studies

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 cecum, colon and prostate. The degree of antiproliferative activity is variable.

Roferon-A can produce clinically meaningful tumour regression or disease stabilization in patients with hairy cell leukaemia and patients with AIDS-related Kaposi's sarcoma. Roferon-A is also effective for the treatment of patients with multiple myeloma. Roferon-A may be active in patients with progressive cutaneous T-cell lymphoma who are refractory to, or unsuitable for, conventional therapy.

Chronic Myelogenous Leukaemia (CML)

Roferon-A is effective for the treatment of patients with chronic phase Philadelphia chromosome-positive CML. Roferon-A produces haematological remission in 60% of patients with chronic phase CML, independent of prior treatment. Two thirds of these patients have complete haematological responses as late as 18 months after treatment started. Furthermore, in contrast to cytotoxic chemotherapy, interferon alfa-2a is able to generate sustained, ongoing cytogenetic responses beyond 40 months. Roferon-A supplemented with intermittent chemotherapy has been shown to prolong overall survival and delay disease progression compared with patients treated with chemotherapy alone.

Roferon-A is effective in the treatment of excessive thrombocytosis in CML and other myeloproliferative diseases. In patients with CML who develop thrombocytosis, Roferon-A lowers the platelet count within a few days, together with the frequency of associated thrombo-haemorrhagic complications, and has no leukaemogenic potential.

Non-Hodgkin's Lymphoma

Roferon-A prolongs disease-free and progression-free survival when used as adjunctive treatment to chemotherapy (with or without radiotherapy) in patients with low-grade non-Hodgkin's lymphoma.

Renal Cell Carcinoma (RCC)

In patients with advanced renal cell carcinoma, Roferon-A in combination with vinblastine has shown survival advantage over chemotherapy alone.

Study BO17705: BO17705 was a multicentre, randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of Roferon-A in combination with bevacizumab (Avastin[®]) versus Roferon-A alone as first-line treatment in metastatic RCC. Roferon-A (9 MIU three times a week) plus Avastin (10 mg/kg every two weeks) or placebo was given until disease progression. A lower starting Roferon-A dose (3 or 6 MIU) was permitted as long as the recommended 9 MIU dose was reached within the first 2 weeks of treatment. If 9 MIU was not tolerated, Roferon-A dosage reduction to a minimum of 3 MIU three times a week was also permitted.

In this study a benefit to patients with advanced and/or metastatic RCC was shown. A clinically relevant and statistically significant increase in progression-free survival, a trend towards an increase in overall survival and a statistically significant increase in the percentage of responders in the Avastin + Roferon-A arm compared with the placebo + Roferon-A arm were observed. However, the observed increase of 2 months in overall survival was not significant. The efficacy results are presented in Table 1.

Table 1: Efficacy Results for Study BO17705

	BO17705	
	Roferon-A + Placebo	Roferon-A + Avastin
Number of Patients	322	327
<u>Progression-Free Survival</u>		
Median (months)	5.4	10.2
Hazard ratio [95% CI]	0.63 [0.52; 0.75] (<i>p</i> -value < 0.0001)	
<u>Objective Response Rate (%) in Patients with Measurable Disease</u>		
<i>n</i>	289	306
Response rate	12.8 %	31.4 %
	(p-value < 0.0001)	
<u>Overall Survival</u>		
Median (months)	21.3	23.3
Hazard ratio [95% CI]	0.91 [0.76; 1.10] (<i>p</i> -value = 0.3360)	

Ninety seven (97) patients in the Roferon-A arm and 131 patients in the Avastin arm reduced the dose of Roferon-A from 9 MIU to either 6 or 3 MIU three times a week as pre-specified in the protocol.

For more information on the combination use with Avastin, refer to the Avastin Data Sheet.

Malignant Melanoma

Patients with advanced malignant melanoma have shown objective regression of cutaneous and visceral tumours on Roferon-A therapy. Roferon-A is also of benefit in extending the period of

disease-free survival in patients who have had a malignant melanoma (tumour thickness > 1.5mm) surgically removed and who have no nodal or distant metastases before treatment commences.

Chronic Hepatitis B and C

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

Condylomata Acuminata

Roferon-A is effective in the treatment of condylomata acuminata.

Pharmacodynamic Properties

No information available.

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.

Pharmacokinetics in special populations

The pharmacokinetics of interferon alfa-2a after single im 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 three times a week (1 – 136 MIU) dosing for up to 28 days.

Intramuscular administration of Roferon-A one or more times daily for up to 28 days has resulted in peak plasma concentrations 2 – 4 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 ribavirin prescribing information.

Pharmaceutical Particulars

Stability

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

Special Remarks

Special precautions for storage

Pre-filled syringes: Store at 2 – 8°C; do not freeze. Store container in outer carton to protect from light.

Instructions for use, handling and disposal

Pre-filled syringes

Roferon-A 3 MIU, 6 MIU and 9 MIU pre-filled syringes are for single-dose use.

Parenteral products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

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.

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

Medicine Classification

Prescription medicine

Packs

Pre-filled syringes

Roferon-A 3 MIU, 6 MIU or 9 MIU pre-filled syringes containing a ready-to-use solution for injection for single-dose use.

Each pre-filled syringe pack contains:

1 x pre-filled syringe containing 0.5 mL solution for injection

1 x needle 27G (0.4 mm) x 12 mm for sc injection

Name and Address

Roche Products (New Zealand) Limited

PO Box 12492 Penrose

Auckland 1642

NEW ZEALAND

Telephone: (09) 635 1500

Fax: (09) 635 1522

Toll Free: 0800 656 464

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