PRODUCT MONOGRAPH

ROFERON®-A

(interferon alfa-2a)
Solution for Injection

Biological Response Modifier

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DATE OF APPROVAL:
July 22, 2002

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CDS Version 1.0

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NAME OF DRUG

ROFERON®-A
(interferon alfa-2a)
Solution for Injection

THERAPEUTIC CLASSIFICATION

Biological Response Modifier

ACTIONS AND CLINICAL PHARMACOLOGY

The mechanisms by which 'Roferon'-A (interferon alfa-2a), or any other interferon, exerts antitumor activity are not clearly understood. However, it is believed that the direct antiproliferative action against tumor cells and modulation of the host immune response play important roles in the antitumor activity.

'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 immunocompromised (nude) mice.[1]

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

The pharmacokinetics of 'Roferon'-A in man are linear over a 3 to 198 million IU dose range. In healthy people, recombinant interferon alfa-2a exhibited an elimination half-life of 3.7 to 8.5 hours (mean 5.1 hours)[2], volume of distribution at steady-state of 0.223 to 0.748 L/kg (mean 0.400 L/kg) and a total body clearance of 2.14 to 3.62 mL/min/kg (mean 2.79 mL/min/kg) after a 36 million IU (2.2×10^8 pg) intravenous infusion. Renal catabolism is the major pathway for 'Roferon'-A elimination; biliary excretion and liver metabolism are minor pathways. After intramuscular and subcutaneous administrations of 36 million IU, peak serum concentrations ranged from 1,500 to 2,580 pg/mL (mean 2,020 pg/mL) at a mean time to peak of 3.8 hours and from 1,250 to 2,320 pg/mL (mean 1,730 pg/mL) at a mean time to peak of 7.3 hours, respectively.[2] The apparent fraction of the dose absorbed after intramuscular or subcutaneous injection was greater than 80%.

The pharmacokinetics of recombinant interferon alfa-2a after single intramuscular doses to patients with disseminated cancer and chronic hepatitis B were similar to those found in healthy volunteers. Dose proportional increases in serum concentrations were observed after single doses up to 198 million IU. There were no changes in the distribution or elimination of recombinant interferon alfa-2a during twice daily (0.5 to 36 million IU), once daily (1 to 54 million IU), or three times weekly (1 to 136 million IU) dosing regimens up to 28 days of dosing. Multiple intramuscular doses of recombinant interferon alfa-2a resulted in an accumulation of 2 to 4 times the single dose serum concentrations. Pharmacokinetic information in patients with hairy cell leukemia is presently unknown.

INDICATIONS

'Roferon'-A (interferon alfa-2a) is indicated for use in the treatment of:

Hairy Cell Leukemia[3,4]
Kaposi's Sarcoma in patients with AIDS (Acquired Immune Deficiency Syndrome)[5,6]
Chronic Active Hepatitis B[9,10]
Chronic Myelogeneous Leukemia [11,12] (CML) and Thrombocytosis associated with CML[13]
Renal Cell Carcinoma[14,15]
Cutaneous T-Cell Lymphoma [16,17] (CTCL)
Chronic Hepatitis C [18,19]

CONTRAINDICATIONS

'Roferon'-A (interferon alfa-2a) is contraindicated in patients with known hypersensitivity to the drug, its components or other interferon preparations.

'Roferon'-A Solution, which contains benzyl alcohol as a preservative, is contraindicated in patients with hypersensitivity to benzyl alcohol. Also see PRECAUTIONS, Use in Children.

'Roferon'-A is also contraindicated in patients with chronic hepatitis associated with advanced, decompensated cirrhosis of the liver and in patients with chronic hepatitis who are being or have recently been treated with immunosuppressive agents, excluding short-term "steroid withdrawal".

WARNINGS

Initial therapy with 'Roferon'-A (interferon alfa-2a) should be conducted under the guidance of a qualified physician experienced in the use of cancer chemotherapeutic agents, in a unit having adequate facilities for monitoring of the relevant clinical and laboratory parameters.

Treatment with 'Roferon'-A is not recommended in patients with severe preexisting cardiac disease or severe renal, hepatic or myeloid dysfunction as the benefit-risk ratio may not warrant therapy.

Alfa Interferons 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 cases, but not all cases, these disorders resolve after stopping interferon therapy.

PRECAUTIONS

General: If acute hypersensitivity reactions to 'Roferon'-A (interferon alfa-2a) develop, the drug should be discontinued.

Moderate to severe adverse reactions may require modification of the patient's dosage regimen, or in some cases, termination of 'Roferon'-A therapy.

Central nervous system adverse reactions have been reported. These reactions included confusion, somnolence, dizziness and depression. Seizures and coma have been rarely observed. Most of these abnormalities were mild and were reversible within a few days to a few weeks upon dose reduction or discontinuation of `Roferon'-A therapy. `Roferon'-A should be used with caution in patients with seizure disorders and/or compromised central nervous system functions. Periodic examination of the neuropsychiatric status of all patients is recommended.

'Roferon'-A should be administered with caution to patients with 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 (ie. fever, chills), frequently associated with `Roferon'-A administration may exacerbate pre-existing cardiac conditions. Myocardial infarction occurred rarely in patients receiving 'Roferon'-A.

Those patients who have preexisting cardiac abnormalities and/or are in advanced stages of cancer should have electrocardiograms taken prior to and during the course of treatment.

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

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 has been rarely associated with exacerbation or provocation of psoriasis and with severe hepatic dysfunction and liver failure.

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 should have their blood glucose measured and adjusted according to their antidiabetic regimen.

Careful periodic monitoring of all patients is recommended. Suicidal behavior has been observed rarely in patients receiving 'Roferon'-A. Therapy should be discontinued in patients exhibiting suicidal behavior.

The development of auto-antibodies may play a role in the development of autoimmune disorders. Autoimmune phenomena such as vasculitis, arthritis, hemolytic anemia, thyroid dysfunction and lupus erythematosus syndrome have been observed rarely in patients receiving 'Roferon'-A. These occur more frequently in subjects predisposed to the development of autoimmune disorders.

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.

Use in Pregnancy: Safe use in human pregnancy has not been established. As with other anticancer drugs, 'Roferon'-A should not be administered to fertile persons of either sex not practising effective contraception. In pregnancy, 'Roferon'-A should be administered only if the benefit to the woman justifies the potential risk to the foetus (see Reproductive Studies).

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.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to postpone treatment, taking into account the importance of the drug to the mother.

Use in Children: Safety and effectiveness in patients under 18 years of age have not been established. '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.

Patients with Special Diseases: Caution should be exercised when administering `Roferon'-A to patients with severe myelosuppression.

Drug Interactions: Interactions between `Roferon'-A and other drugs have not been fully evaluated.

As 'Roferon'-A may affect central nervous functions, interactions could occur following concurrent administration of centrally-acting drugs.

Alfa-Interferons may effect the oxidative metabolic process by reducing the activity of microsomal cytochrome enzymes in the P450 group. Although the clinical relevance is still unclear, this should be taken into account when prescribing concomitant therapy with drugs metabolized by this route. Reduced clearance of theophylline following the concomitant administration of alfa-interferons has been reported.
It has been observed that the neurotoxic, hematotoxic or cardiotoxic effects of previously or concurrently administered drugs may be incresed by interferons. Interactions could occur following concurrent administration of centrally-acting drugs.

Caution should be exercised when 'Roferon'-A is used in combination with other agents that are known to cause myelosuppression. Synergistic toxicity has been observed when 'Roferon'-A is administered in combination with zidovudine (AZT). The effects of 'Roferon'-A when combined with other drugs used in the treatment of AIDS-related diseases are not known.

Laboratory Tests: Periodic complete blood counts and liver function tests should be performed during the course of `Roferon'-A treatment. They should be performed prior to therapy and at appropriate periods during therapy. Interferon has suppressive effect on the bone marrow, leading to a fall in the white blood count, particularly the granulocytes, the platelet count and commonly the hemoglobin concentration.

Information to be Provided to the Patient: Patients should be informed not only of the potential benefits and risks of therapy, but also that they will probably experience adverse reactions.

Patients should be well hydrated, especially during the initial stages of treatment.

ADVERSE REACTIONS

The following data on adverse reactions are based on information derived from the treatment of patients with a wide variety of malignancies including patients with hairy cell leukemia, AIDS related Kaposi's Sarcoma, and patients with chronic active hepatitis B[7] and patients with chronic hepatitis C. Most patients suffered from advanced forms of the diseases.

General Symptoms: The majority of the patients experienced flu-like symptoms such as fatigue, fever, chills, anorexia, myalgia, headache, arthralgia and diaphoresis. These acute side effects can usually be reduced or eliminated by concurrent administration of acetaminophen and tend to diminish with continued therapy or dose moderation. Continuing therapy can lead to lethargy, weakness and fatigue.

Gastrointestinal Tract: Slightly more than half of the patients studied experienced anorexia and/or nausea. Emesis, diarrhea and mild to moderate abdominal pain were less frequently observed. Constipation, flatulence, hypermotility or heartburn occurred rarely. Reactivation of peptic ulcer and non life-threatening gastrointestinal bleeding have also been reported.

Alterations of hepatic function shown by an elevation of AST, alkaline phosphatase, LDH and bilirubin have been uncommon and generally did not require dose adjustment. Hepatitis was rarely reported.

Central Nervous System: Dizziness, vertigo, decreased mental status, forgetfulness, depression, drowsiness, confusion, behavioural disturbances such as anxiety and nervousness and sleep disturbances were reported. Severe somnolence, convulsions, coma, cerebrovascular adverse events, seizures, encephalopathy, transient impotence and suicidal behavior are rare complications.

Peripheral Nervous System: Paresthesias, sleep disturbances, visual disturbances, numbness, neuropathy and tremor occurred occasionally, and ischemic retinopathy rarely.

Cardiovascular and Pulmonary Systems: Reactions were seen in less than a fifth of the patients and consisted of transient hypotensive or hypertensive episodes, edema, chest pain, cyanosis, arrhythmias and palpitations. Rare cases of coughing, mild dyspnea, pulmonary edema, congestive heart failure, cardiorespiratory arrest and myocardial infarction have been reported. Cardiovascular problems are very rarely seen in patients with hepatitis B.

Skin and Appendages: Mild to moderate hair loss occurred in up to one fifth of patients, but this was reversible on discontinuation of treatment. Rash, pruritus, dryness of skin and mucous membranes, rhinorrhea, urticaria, epistaxis and reactivation of herpes labialis were reported rarely.

Renal and Urinary System: Abnormalities consisted primarily of proteinuria and increased red and white cell counts in sediment. Electrolyte disturbances, generally in association with anorexia or dehydration, elevations of BUN, serum creatinine and uric acid have been rarely observed. Rare cases of acute renal failure have been reported, mainly in cancer patients with renal disease and/or nephrotoxic comedications as concomitant risk factors.

Hematopoietic System: Transient leukopenia occurred in about one third of the patients, but rarely required dosage reduction.

Thrombocytopenia and decreased hemoglobin in myelosuppressed patients and thrombocytopenia in non-myelosuppressed patients was less frequently seen. Decreased hemoglobin and hematocrit occurred rarely. Recovery of severe hematological deviations to pre-treatment levels usually occurred within seven to ten days after stopping `Roferon'-A (interferon-alfa-2a) treatment.

Other: Weight loss, change in taste, dry mouth, dryness or inflammation of the oropharynx have been reported, injection site reactions, bleeding gums, eccymosis, and pneumonia rarely. Hyperglycemia has been observed rarely in patients treated with ‘Roferon’-A. Asymptomatic hypocalcemia has been reported very rarely.

Neutralizing Antibodies to `Roferon'-A were detected in 14.6 -38.0% of patients in clinical trials with Hairy Cell Leukemia, AIDS Related Kaposi's Sarcoma, Chronic Active Hepatitis B, Renal Cell Carcinoma, Chronic Myelogeneous Leukemia and Chronic Hepatitis C.

No data on neutralizing antibodies yet exist from clinical trials in which the presently marketed material, which is stored at 4°C, has been used. In a mouse model, however, the relative immunogenicity of ‘Roferon’-A increases with time when the material is stored at 25°C-no such increase in immunogenicity is observed when 'Roferon'-A is stored at 4°C, the presently recommended storage conditions.

In general, the higher the cumulative dose of 'Roferon'-A received, the more likely a patient will produce antibodies to 'Roferon'-A. Antibodies to human leukocyte interferon may occur spontaneously in certain clinical conditions (cancer, systemic lupus erythematosus, herpes zoster) in patients who have never received exogenous interferon.[8]

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

DOSAGE

The following dosage schedules are recommended and should not be exceeded:

Adults:

HAIRY CELL LEUKEMIA — Induction dose of 3 million IU daily for 16 to 24 weeks administered as an intramuscular injection. Maintenance 3 million IU three times per week. Subcutaneous administration may be utilized in thrombocytopenia patients (platelet count < 50,000) or in patients at risk for bleeding.

AIDS RELATED KAPOSI'S SARCOMA — Induction dose of 36 million IU daily for four to ten weeks as a subcutaneous or intramuscular injection. Maintenance dose of 36 million IU three times per week.

Patients with Kaposi's sarcoma should be treated for 30 to 90 days before physician determines the possible benefits of continued therapy in the patients whose disease did not progress.

CHRONIC ACTIVE HEPATITIS B — Recommended dose is 4.5 million IU administered subcutaneously three times per week for six months.

If markers for viral replication or HB_eAg 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 three to four months of treatment, discontinuation of therapy should be considered.

Therapeutic trials in patients with chronic active hepatitis B show that 'Roferon'-A (interferon alfa-2a) therapy at doses equivalent to $\geq$4.5 million IU three times weekly for 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 generally 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 antigenemia 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 ALAT levels. Doses $\leq$1.5 million IU three times weekly for 16 weeks are suboptimally effective. Some patients may require doses up to the equivalent of 18 million IU for six months to benefit from therapy.

CHRONIC MYELOGENEOUS LEUKEMIA — It is recommended that 'Roferon'-A should be given by subcutaneous or intramuscular injection for eight to twelve weeks to patients 18 years or more. The recommended schedule is:

3 million IU daily	Days 1-3
6 million IU daily	Days 4-6
9 million IU daily	Days 7-84

Duration of Treatment:
Patients should be treated for a minimum of eight weeks, preferably for at least twelve weeks before the physician decides whether or not 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 response is achieved or for a maximum of 18 months. All patients with complete hematologic responses should continue treatment with 9 million IU daily (optimum) or 9 million IU three times a 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 two years after treatment start.

THROMBOCYTOSIS ASSOCIATED WITH CML — Thrombocytosis is a frequent concomitant phenomenon in CML. The morbid nature of severe thrombocytosis is reflected by the frequent manifestation of a serious thrombotic or hemorrhagic diathesis. In a large Phase 3 clinical trial, when 206 interferon alfa-2a treated CML patients were available for hematologic response assessment, 75 subjects had a baseline thrombocyte count of $> 450 \times 10^9$/L. Platelet control was achieved in 73 patients (97%).

Therefore, therapy is recommended with interferon alfa-2a for the treatment of patients with excessive thrombocytosis in CML, even in the absence of cytogenetic response.

The recommended dosage for thrombocytosis in CML is the same as that recommended above for the treatment of CML.

RENAL CELL CARCINOMA - Induction dose of a least 18 million IU daily as a subcutaneous or intramuscular injection and if possible, 36 million IU daily for eight to twelve weeks using the recommended escalation schedules:

3 million IU daily	Days 1-3

9 million IU daily	Days 4-6
18 million IU daily	Days 7-9 and if tolerated, increase to:
36 million IU daily	Days 10-84

Maintenance doses should be given to those patients responding to induction therapy. The maintenance dose should be identical to the maximum tolerated dose but should not exceed 36 million IU three times per week.

'Roferon'-A has also shown to be effective in combination with vinblastine. 18 million IU of 'Roferon'-A given intramuscularly three times per week for eight to twelve weeks with concurrent vinblastine intravenously injected with doses of 0.1 mg/kg body weight, once every three weeks has shown increased effectiveness over 'Roferon'-A alone at these relatively lower doses. However, the objective response rate of the combination was similar to the response rate under optimal conditions for treatment of 'Roferon'-A alone.

CUTANEOUS T-CELL LYMPHOMA - Induction dose of at least 18 million IU daily for 8-12 weeks administered by subcutaneous or intramuscular injections. The recommended escalation schedule is as follows:

3 million IU daily	Days 1-3
9 million IU daily	Days 4-6
18 million IU daily	Days 7-84

Maintenance dose of 18 million IU three times per weeks. Patients should be treated for a minimum of eight weeks and preferably for at least twelve weeks before the physician decides whether to continue treatment in responding patients or to discontinue treatment in nonresponding patients. Minimum treatment duration for patients who respond is suggested to be 12 months in order to maximize the chance of achieving a complete response and improve the chance of a prolonged response. Patients have been treated for up to 40 consecutive months.

In clinical trials, fifty-five of 85 evaluable patients with CTCL received the recommended dosage regimen and the following objective responses were observed:

	Stage I or II CTCL (n=37)	**Stage III or IV CTCL (n=18)**
Overall Response 95% C.I.	73% 56-86%	39% 17-64%
Complete Response 95% C.I.	35% 20-53%	6% ___
Partial Response 95% C.I.	38% 22-55%	33% 13-59%

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 amino transferase (ALT) without liver decompensation (Child's Class A).
Initial Dosage:

'Roferon'-A should be administered at a dose of 6 MIU by subcutaneous or intramuscular injection three times a week for three months as induction therapy.

Maintenance Dosage:

Patients whose serum ALT has normalized require maintenance therapy with 3 MIU 'Roferon'-A three times a week for an additional three months to consolidate the complete response.

Patients whose serum ALT has not normalized should stop treatment.

Note: The majority of patients who relapse after adequate treatment do so within four months of the end of treatment.

SPECIAL DOSAGE INSTRUCTIONS

Dosage should be modified to take into account the constitutional symptoms, the myelosuppressive effects, and the other clinical or laboratory test abnormalities caused by 'Roferon'-A (interferon alfa-2a) therapy.

Dosage adjustments may be more important when administering 'Roferon'-A to patients receiving concomitant therapies or who may have compromised bone marrow reserve due to prior x-ray treatment or chemotherapy.

Elderly: Elderly patients may be more susceptible to the side effects and caution is recommended in the treatment of such patients.

Children: Safety and efficacy in patients under 18 years of age have not been established.

ADMINISTRATION

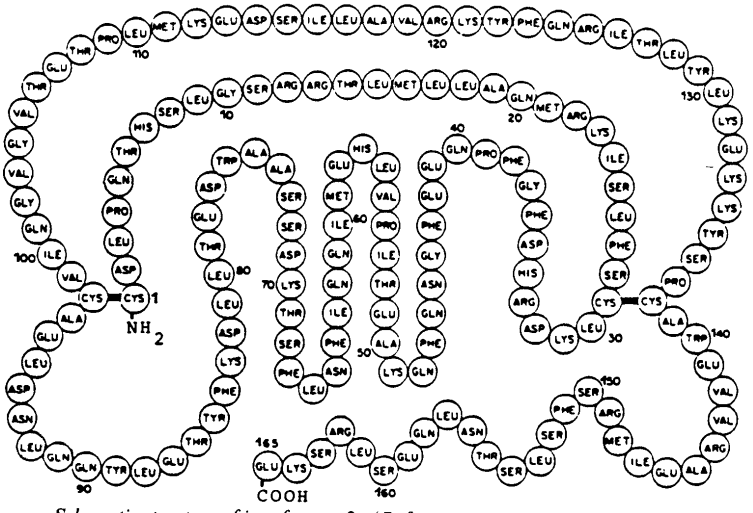
The subcutaneous or intramuscular routes of administration should be used. Subcutaneous administration is particularly suggested for, but not limited to, patients who are thrombocytopenic (platelet count < 50,000) or who are at risk for bleeding. See also INFORMATION FOR THE PATIENT for information on self-administration.

PHARMACEUTICAL INFORMATION

(i) Drug Substance: 'Roferon'-A (interferon alfa-2a) is a highly purified protein containing 165 amino acids. It is produced by recombinant DNA technology using genetically engineered E. coli strain containing DNA that codes for the human protein.

Proper Name: Interferon alfa-2a, recombinant.

Structural Formula:



Schematic structure of interferon α-2a (Roferon-A).

Molecular Weight: Approximately 19,000 daltons.

Physical Form: A water soluble protein.

(ii) Dosage Forms and Composition:

'Roferon'-A Solutions

3 million IU/1 mL Vial:
Each mL contains 3 million IU interferon alfa-2a. Non-medicinal ingredients: each mL contains 7.21 mg sodium chloride, 0.77 mg ammonium acetate, 0.2 mg polysorbate 80 with 10.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

9 million IU/1 mL Vial:
Each mL contains 9 million IU interferon alfa-2a. Non-medicinal ingredients: each mL contains 7.21 mg sodium chloride, 0.77 mg ammonium acetate, 0.2 mg polysorbate 80 with 10.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

9 million IU/0.9 mL Vial (multiple dose vial):
Each 0.9 mL contains 9 million IU interferon alfa-2a. Non-medicinal ingredients: each 0.9 mL contains 6.49 mg sodium chloride, 0.69 mg ammonium acetate, 0.18 mg polysorbate 80 with 9.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

18 million IU/3 mL Vial (multiple dose vial):
Each mL contains 6 million IU interferon alfa-2a. Non-medicinal ingredients: each mL contains 7.21 mg sodium chloride, 0.77 g ammonium acetate, 0.2 mg polysorbate 80 with 10.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

36 million IU/1 mL Vial:
Each mL contains 36 million IU interferon alfa-2a. Non-medicinal ingredients: each mL contains 7.21 mg sodium chloride, 0.77 mg ammonium acetate, 0.2 mg polysorbate 80 with 10.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

'Roferon'-A Pre-filled Syringe:

3 million IU/0.5 mL pre-filled syringe:
Each 0.5mL contains 3 million IU interferon alfa-2a. Non-medicinal ingredients: each 0.5mL contains 3.605 mg sodium chloride, 0.385 mg ammonium acetate, 0.1 mg polysorbate 80 with 5.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

4.5 million IU/0.5 mL pre-filled syringe:
Each 0.5 mL contains 4.5 million IU interferon alfa-2a. Non-medicinal ingredients: each 0.5 mL contains 3.605 mg sodium chloride, 0.385 mg ammonium acetate, 0.1 mg polysorbate 80 with 5.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

6 million IU/0.5 mL pre-filled syringe:

Each 0.5 mL contains 6 million IU interferon alfa-2a. Non-medicinal ingredients: each 0.5 mL contains 3.605 mg sodium chloride, 0.385 mg ammonium acetate, 0.1 mg polysorbate 80 with 5.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

9 million IU/0.5 mL pre-filled syringe:
Each 0.5 mL contains 9 million IU interferon alfa-2a. Non-medicinal ingredients: each 0.5 mL contains 3.605 mg sodium chloride, 0.385 mg ammonium acetate, 0.1 mg polysorbate 80 with 5.0 mg benzyl alcohol as preservative and sodium hydroxide or glacial acetic acid to adjust pH.

(iii) Stability and Storage Recommendations:

'Roferon'-A Solutions
See expiration date on the outer package. Do not use past the expiration date. Store in a refrigerator at 2 to 8°C. Protect from light. Do not freeze or shake. Multiple dose vials (9 million IU/0.9 mL and 18 million IU/3 mL) should be used within 30 days of the first withdrawal.

'Roferon'-A Pre-filled Syringe:
See expiration date on the outer package. Do not use past the expiration date. Store in a refrigerator at 2 to 8°C. Do not freeze. Protect from light.

AVAILABILITY OF DOSAGE FORMS

'Roferon'-A (interferon alfa-2a) Solution
- Vials containing 3 million IU interferon alfa-2a in 1 mL.
- Vials containing 9 million IU interferon alfa-2a in 1 mL.
- Vials (multiple dose) containing 9 million IU interferon alfa-2a in 0.9 mL.
- Vials (multiple dose) containing 18 million IU interferon alfa-2a in 3 mL.
- Vials containing 36 million IU interferon alfa-2a in 1 mL.

'Roferon'-A Pre-filled Syringe:
- 1 pre-filled syringe containing 3 million IU interferon alfa-2a in 0.5 mL plus 1 needle for s.c. injection.
- 1 pre-filled syringe containing 4.5 million IU interferon alfa-2a in 0.5 mL plus 1 needle for s.c. injection.
- 1 pre-filled syringe containing 6 million IU interferon alfa-2a in 0.5 mL plus 1 needle for s.c. injection.
- 1 pre-filled syringe containing 9 million IU interferon alfa-2a in 0.5 mL plus 1 needle for s.c. injection.

INFORMATION FOR THE PATIENT

Instructions for self-administration:
'Roferon'-A is injected into the tissue just under the skin. This is known as subcutaneous injection. Usually 'Roferon'-A is administered 3 times a week. You should inject approximately the same time every day. The most suitable places for injection are the top of the thighs and the abdomen, except for the belly button area (see illustration A).

Rotate injection site to avoid the risk of soreness at any one site.

1. Before preparing the syringe
- Do not use 'Roferon'-A after the expiry date shown on the pre-filled syringe label.
- Check the dose that you have been prescribed.
- Check the liquid has no discolouration, cloudiness or particles.
- Let the syringe stand for 30 minutes at room temperature.
- Wash your hands thoroughly.
- Place everything you need within easy reach: syringe, needle and alcohol wipes.

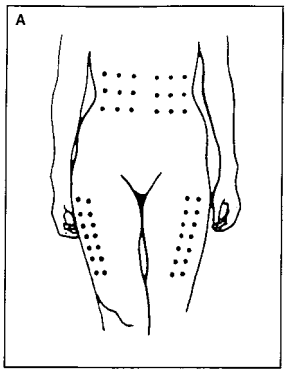
2. How to prepare the syringe
(See illustration on the inner side of the box)
- Take the sealed needle in both hands and snap the coloured cap backwards. Remove the coloured cap. ***Do not*** remove the plastic needle shield (steps 1 and 2).
- Remove the rubber tip from the syringe (step 3).
- Attach the needle with the plastic shield firmly to the syringe (step 4).
- Remove the plastic cover from the needle while holding the coloured fitting hub. Avoid pushing the plunger stopper (step 5).

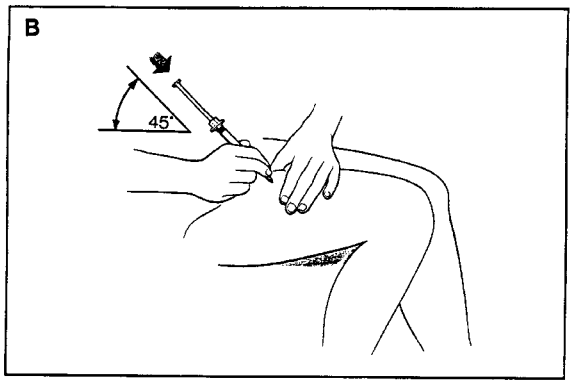
The syringe is now ready for use.

3. How to inject 'Roferon'-A
(See illustration B)
- Disinfect the skin using an alcohol wipe and pinch the skin between the thumb and forefinger, without squeezing.
- Insert the needle fully into the skin at an angle of approximately 45°. Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, remove the needle and insert it in another place.
- Inject the liquid slowly and continuously, keeping the skin pinched.
- After injecting remove the needle and release the skin. Disinfect the skin with a clean alcohol wipe.

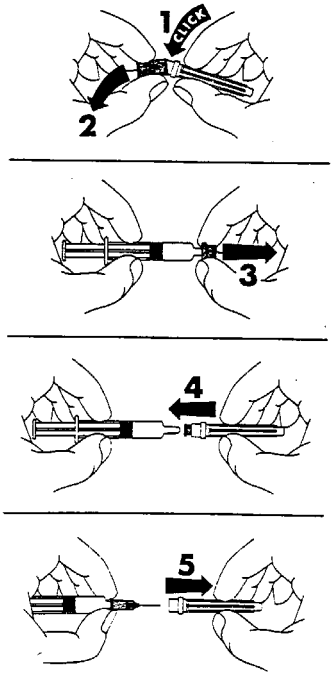
Remember: Most people can learn to give themselves a subcutaneous injection, but if you experience difficulty, please do not be afraid to ask for help and advice from your doctor, nurse or pharmacist.

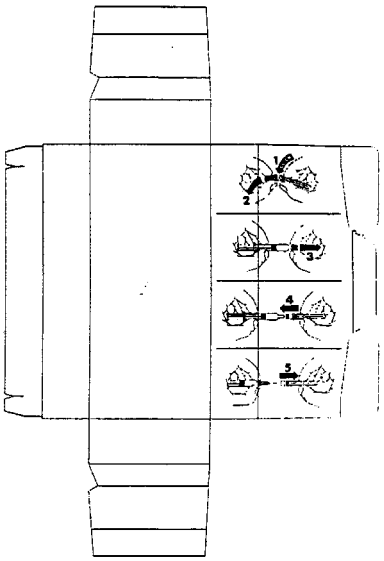
4. How to dispose of used syringes
Never put used syringes into your normal household waste bin. ***Consult your doctor or pharmacist*** for the proper disposal of 'Roferon'-A syringes.





Instructions printed on the inside of the box.





PHARMACOLOGY

Animal: Following administration of interferon alfa (IFN∝) to human tumor cells, reduction of DNA, RNA and protein synthesis have been observed. However, changes in cellular protein induced by IFN∝ are probably more complex than an inhibition of synthesis, as initiation or augmentation of protein synthesis have also been observed. The activity of IFN∝ on the proliferation capacity of human tumor cells has been tentatively correlated with the number of IFN∝ receptors on these cells. The variations in sensitivity may be partly due to the different numbers of receptors for IFN∝ found on the tumor cells.

The antiproliferative effects of interferon alfa-2a against numerous human cell lines in vitro have been extensively investigated. Tables 1 and 2 list the concentrations of interferon alfa-2a required to inhibit the proliferation of a series of cell lines grown in suspension and monolayer, respectively.

TABLE 1: Antiproliferative effect of 'Roferon'-A (interferon alfa-2a) on suspension culture cell lines derived from human malignant hematopoietic tumors

Cell Line	Origin	Cell Number * ($x10^{-4}$)		Concentration for 50% Growth Inhibition (U/mL)
		Initial (Day 0)	Control (Day 5)	
Daudi	Burkitt's lymphoma	4.0	16.3	19.5
RPMI-8226	Myeloma	1.0	7.6	69.2
MOLT-4	Acute lymphoblastic leukemia (T cell)	1.0	28.2	324
U937	Histiocytic lymphoma	1.0	33.9	389
CCRF-HSB-2	Acute lymphoblastic leukemia (T cell)	1.0	23.3	525
RPMI-6402	Acute lymphoblastic leukemia (T cell)	1.0	33.9	1,260
BALL-1	Acute lymphoblastic leukemia (B cell)	1.0	6.0	1,290
Namalwa	Burkitt's lymphoma	1.0	5.7	> 10,000

* The number of cells per mL at the beginning of culture (Initial) and after 5-day culture without 'Roferon'-A (Control).

TABLE 2: Antiproliferative effect of 'Roferon'-A on monolayer culture cell lines derived from human malignant solid tumors

Cell Line	Origin	Cell Number * ($x10^{-4}$)			Concentration for 50% Growth Inhibition (U/mL)
		Seeded (Day 0)	Initial (Day 0+4-hr)	Control (Day 5)	
PC-93	Prostatic carcinoma	2.0	1.8	10.0	< 10
HT-1080	Fibrosarcoma	1.0	1.1	10.7	< 10
PC-3	Prostatic carcinoma	5.0	4.2	27.9	49
NC 65	Renal cancer	2.0	1.7	19.4	91
T 24	Astrocytoma	1.0	1.6	203.5	102
KB	Oral carcinoma	1.0	0.9	40.4	115
PLC/PRF/5	Hepatoma	8.0	7.8	60.7	129
SW-13	Adrenal adenocarcinoma	5.0	5.7	29.7	162
HeLa	Cervix carcinoma	1.0	1.1	72.6	1,070
T-24	Bladder carcinoma	2.0	2.8	30.4	1,150
Ca SKi	Cervical carcinoma	3.0	3.3	34.9	1,200
HEp-2	Laryngeal carcinoma	1.0	0.9	42.2	1,230
GOTO	Neuroblastoma	5.0	4.0	56.8	1,380
G-361	Melanoma	4.0	3.2	21.2	1,480
GOLO-205	Colon adenocarcinoma	1.0	0.9	37.7	1,550
A549	Lung carcinoma	1.0	1.2	117.5	2,000
PANC-1	Pancreatic Cancer	1.0	1.3	14.4	4,900
G-292	Osteosarcoma	8.0	4.2	42.9	5,370
HT-1376	Bladder carcinoma	5.0	5.7	30.3	5,890
G-401	Wilms's tumor	5.0	4.4	33.2	9,550
ZR-75-1	Breast carcinoma	3.0	2.4	6.6	> 10,000

* The number of seeded cells per dish (Seeded) and the number of recovered cells per dish at the time of fluid change to 'Roferon'-A containing medium 4-5 hr after seeding (Initial) or at the end of 5-day culture without 'Roferon'-A (Control).

These data indicate that 'Roferon'-A has pronounced growth inhibiting effects against some but not all human tumor cells lines in vitro.

TOXICOLOGY

Acute Toxicity

The results of parenteral LD_{50} studies are summarized below:

LD_{50}values (in million IU/kg):

	i.v.	i.m.	s.c.
Mouse	>250	> 500	>30
Rat	>100	> 100	>30
Ferret		> 30	>30
Rabbit	>100	> 100	>30

Long-Term Toxicology

Long-term toxicity studies were done in mice, rats, and monkeys. The species, duration and route of administration and maximum dose administered are shown in the following table:

Species	Route of Administration	Maximum Dose Units/kg/day	Duration Weeks
Mice	I.M.	5.7×10^6	5
Rats	I.V.	1×10^8	5
	I.M.	1×10^8	5
	I.M.	3×10^7	26
Monkeys (Cynomolgus)	I.V./I.M.	1×10^6	1
		10×10^6	1
Monkeys (Squirrels)	I.M.	2.5×10^6	2
Monkeys (Cynomolgus)	I.M.	10×10^6	13
Monkeys (Rhesus)	I.M.	25×10^6	4

The following summary of the long-term toxicity studies is provided:

Intramuscular administrations up to 5.7×10^6 IU/kg/day for five weeks were tolerated well by mice, except for dose-related but reversible increases in platelets and WBC at 2.85 and 5.7×10^6 IU/kg/day.

In a five-week intravenous toxicity study in rats, the only finding was a very slight inhibition in body weight gain in the females receiving the highest dose of 1 x 10^8 IU/kg/day.

In a five-week intramuscular toxicity study in rats, doses up to 1 x 10^8 IU/kg/day were tolerated without any side effects.

In a six-month intramuscular toxicity study in rats, daily doses up to 3 x 10^7 IU/kg were tolerated without any side-effects.

Seven intramuscular or intravenous injections of 1 x 10^6 or 1 x 10^7 IU/kg were tolerated well by cynomolgus monkeys. The only finding was a transient elevation of the GOT, which was more pronounced in treatment animals than in controls.

A two-week intramuscular toxicity study in squirrel monkeys produced no side-effects with 2.5 x 10^6 IU/kg/day except a slight, reversible decrease in the mean hemoglobin concentration and the mean hematocrit value.

In a 13-week intramuscular toxicity study in cynomolgus monkeys, a slight transient decrease in body weight and food consumption in the second and third study weeks and a slightly increased body temperature in animals receiving the highest dose of 10 x 10^6 IU/kg/day (reversible after five weeks recovery) were found.

In a four-week intramuscular toxicity study in rhesus monkeys given daily doses of up to 25 x 10^6 IU/kg, adverse effects were limited to anorexia and associated weight loss.

Genotoxicity Studies

Ames Test
The mutagenic potential of interferon alfa-2a was evaluated in an in vitro prokaryotic reversion test using five Salmonella typhimurium mutants: TA 1535, TA 1537, TA 1538, TA 98 and TA 100, as well as E. coli B/r wp2 UV rA with or without metabolic activation. Results were negative in the dose range of 8 to 5,000 µg/plate.

Chromosome Aberrations in Human Lymphocytes
Human lymphocyte cultures were treated with interferon alfa-2a at concentrations of 2,500, 12,500 and 25,000 units/mL for 24 hours. Higher concentrations of the test substance were cytotoxic. There was no increase in the incidence of chromosomal damage at the doses indicated.

Forward Mutation in Chinese Hamster V79 Cells
The mutagenic potential of interferon alfa-2a was evaluated at the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus in V79 Chinese hamster cells with and without metabolic activation.

At doses of 1.0 x 10^5 to 2.4 x 10^6 U/mL, the drug showed no mutagenic potential at the specific HGPRT locus of the V79 Chinese hamster cells.

"Treat and Plate" Test with Saccharomyces Cerevisiae D7

The diploid yeast strain Saccharomyces cerevisiae D7 was used to test interferon alfa-2a for mutagenic activity. It was shown that after three hours treatment of D7 cells in the stationary growth phase or after 16 hours treatment of D7 cells in the exponential growth phase with aqueous solutions of the drug at concentrations ranging from 3.6×10^3 to 2.25×10^6 units/mL, no mitotic crossing over at the ade-2 locus, no mitotic gene conversion at the trp-5 locus and no reverse mutation at the ile-1 locus were induced. Presence or absence of a rat S-9 liver homogenate fraction induced by phenobarbital or aroclor did not affect the results.

Unscheduled DNA Synthesis (UDS) Assay Using Human Fibroblasts and Primary Cultures of Rat Hepatocytes

Interferon alfa-2a did not induce DNA damage in this test.

Reproduction and Teratology

In a fertility and reproductive performance study in rats at doses up to 1×10^8 IU/kg/day, interferon alfa-2a did not adversely affect the fertility of the male rats, the course of the pregnancy and/or the status of the offspring.

Teratology studies were done in rabbits at doses up to 1×10^7 IU/kg/day and in rats at doses up to 1×10^8 IU/kg/day. No adverse effects were noted on the mothers or offspring of either species.

A peri- and postnatal study was performed in rats at doses up to 1×10^8 IU/kg/day. No adverse effects were observed on the dams, on delivery, or on the fetuses and their postnatal development. The reproductive performance of the F_1 rats was not affected.

Fertility and Teratology in Rhesus Monkeys

Two studies were carried out to determine the effect on the fertility of rhesus monkeys.
In the first study, males and females were treated with intramuscular doses up to 25×10^6 IU/kg/day. Besides transient body weight decrease in males at 5 and 25×10^6 IU/kg/day, a dose-related depression of sperm-head width was noted in these dose groups (reversible after a four-month recovery period). In females, these doses led to reduced ovulatory activity (reduced progesterone levels, absence of preovulatory luteinizing hormones and estrogens). These findings were reversible within one to nine months after termination of treatment.

The sperm findings in males led to a second study being initiated: males only were treated with 25×10^6 IU/kg/day and mated with untreated females. In contrast to the first study, no respective sperm alterations were noted. The fertility and the progress and outcome of pregnancies (including fetuses) was not affected by treatment.

In a teratology study in rhesus monkeys, initial maternal weight loss and a dose-related increase in the abortion rate was seen at 1, 5 and 25×10^6 IU/kg/day (statistically significant in the high dose group). However, no treatment-related teratogenicity was found on external, internal and skeletal examination of the fetuses.

Pregnancy: A study in pregnant rhesus monkeys treated with 1, 5 or 25 million IU/kg/day of 'Roferon'-A (interferon alfa-2a) in their early to midfetal period (days 22 to 70 of gestation) has failed to demonstrate teratogenic activity for 'Roferon'-A. However, 'Roferon'-A has shown a statistically significant increase in abortifacient activity in rhesus monkeys.

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