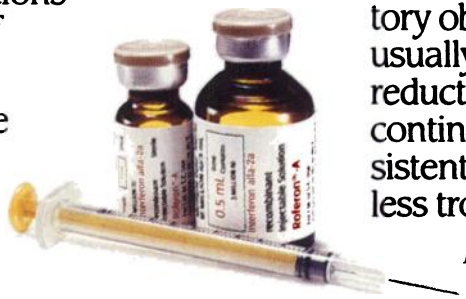
FROM ROCHE RESEARCH

Introducing a new modality in cancer therapy

ROCHE Leading the way in biotherapeutics

a breakthrough in hairy cell leukemia

- ☐ Effective in all stages of the disease.
- ☐ Statistically increased survival compared to a historical control group.
- ☐ Normalizes peripheral blood elements.
- ☐ Improves quality of life.
- ☐ Dramatically decreases the need for red blood cell and platelet transfusions.
- ☐ Virtually eliminates life-threatening opportunistic infections after several months of therapy.
- ☐ Ready-to-use injectable solution. No mixing or reconstitution necessary.
- ☐ SC or IM injection and fixed dosing permit administration without weight or body surface area calculation in home, office or institution.
- ☐ Caution patients not to change brands of Interferon without medical consultation, as a change in dosage may result.
- ☐ Common initial side effects, such as fever, chills, myalgia, headache and fatigue, are self-limiting and generally manageable. Myelosuppression, which can occur early in the treatment course, warrants close clinical and laboratory observation and is usually alleviated by dose reduction or temporary discontinuation of drug. Persistent fatigue is found to be less troublesome with *p.m.* or *h.s.* administration. See following pages for details on all adverse reactions.



Injectable Solution

3 million IU unit-dose vial (3 million IU/mL)	18 million IU multidose vial (3 million IU/0.5 mL)

NEW SC/IM

ROFERON®-A

Interferon alfa-2a, recombinant/Roche

a promise fulfilled

Before prescribing, please see complete product information on following pages.

NEW SC/IM

ROFERON®-A

BRAND OF Interferon alfa-2a, recombinant/Roche

DESCRIPTION: Roferon®-A (Interferon alfa-2a, recombinant/Roche) is a sterile protein product for use by injection. Roferon-A is manufactured by recombinant DNA technology that employs a genetically engineered *E. coli* bacterium containing DNA that codes for the human protein. Interferon alfa-2a, recombinant/Roche is a highly purified protein containing 165 amino acids, and it has an approximate molecular weight of 19,000 daltons. The purification procedure includes affinity chromatography using a murine monoclonal antibody. Roferon-A is supplied as an injectable solution. The solution is colorless and contains Interferon alfa-2a, recombinant/Roche, phenol as a preservative, sodium chloride for isotonicity and human serum albumin as a stabilizer. Fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride, 5 mg/liter. However, the presence of the antibiotic is not detectable in the final product.
Each vial of Roferon-A contains 3 million or 18 million international units (IU) of Interferon alfa-2a, recombinant/Roche. The specific activity of Interferon alfa-2a, recombinant/Roche, is 2×10^8 IU/mg protein. The route of administration is subcutaneous or intramuscular.
CLINICAL PHARMACOLOGY: The mechanism by which Interferon alfa-2a, recombinant/Roche, or any other interferon, exerts antitumor activity is not clearly understood. However, it is believed that direct antiproliferative action against tumor cells and modulation of the host immune response play important roles in the antitumor activity.
The biological activities of Interferon alfa-2a, recombinant/Roche are species-restricted, *i.e.*, they are expressed in a very limited number of species other than humans. As a consequence, preclinical evaluation of Interferon alfa-2a, recombinant/Roche has involved *in vitro* experiments with human cells and some *in vivo* experiments.[1] Using human cells in culture, Interferon alfa-2a, recombinant/Roche has been shown to have antiproliferative and immunomodulatory activities that are very similar to those of the mixture of interferon alfa subtypes produced by human leukocytes. *In vivo*, Interferon alfa-2a, recombinant/Roche has been shown to inhibit the growth of several human tumors growing in immunocompromised (nude) mice. Because of its species-restricted activity, it has not been possible to demonstrate antitumor activity in immunologically intact syngeneic tumor model systems, where effects on the host immune system would be observable. However, such antitumor activity has been repeatedly demonstrated with, for example, mouse interferon-alfa in transplantable mouse tumor systems. The clinical significance of these findings is unknown.
The metabolism of Interferon alfa-2a, recombinant/Roche is consistent with that of alfa interferons in general. Alfa interferons are totally filtered through the glomeruli and undergo rapid proteolytic degradation during tubular reabsorption, rendering a negligible reappearance of intact alfa interferon in the systemic circulation. Small amounts of radiolabeled Interferon alfa-2a, recombinant/Roche appear in the urine of isolated rat kidneys, suggesting near complete reabsorption of Interferon alfa-2a, recombinant/Roche catabolites. Liver metabolism and subsequent biliary excretion are considered minor pathways of elimination for alfa interferons.
The serum concentrations of Interferon alfa-2a, recombinant/Roche reflected a large intersubject variation in both healthy volunteers and patients with disseminated cancer.
In healthy people, Interferon alfa-2a, recombinant/Roche exhibited an elimination half-life of 3.7 to 8.5 hours (mean 5.1 hours), 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. After intramuscular and subcutaneous administrations of 36 million IU, 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. The apparent fraction of the dose absorbed after intramuscular injection was greater than 80%.
The pharmacokinetics of Interferon alfa-2a, recombinant/Roche after single intramuscular doses to patients with disseminated cancer 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 Interferon alfa-2a, recombinant/Roche 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 Interferon alfa-2a, recombinant/Roche 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.
The acute parenteral toxicity of Interferon alfa-2a, recombinant/Roche has been studied in mice, rats, rabbits and ferrets at doses up to 30 million IU/kg intravenously, and 500 million IU/kg intramuscularly. No treatment-related mortality was noted in any species given Interferon alfa-2a, recombinant/Roche by any of the routes of administration.
Effects on Hairy Cell Leukemia: During the first one to two months of treatment of patients with hairy cell leukemia, significant depression of hematopoiesis was likely to occur. Subsequently, there was improvement in circulating blood cell counts.
Of the 75 patients who were evaluable for efficacy following at least 16 weeks of therapy, 46 (61%) achieved complete or partial response. Twenty-one patients (28%) had a minor remission, eight (11%) remained stable, and none had worsening of disease. All patients who achieved either a complete or partial response had complete or partial normalization of all peripheral blood elements including hemoglobin level, white blood cell, neutrophil, monocyte and platelet counts with a concomitant decrease in peripheral blood and bone marrow hairy cells. Responding patients also exhibited a marked reduction in red blood cell and platelet transfusion requirements, a decrease in infectious episodes and improvement in performance status. The probability of survival for two years in patients receiving Roferon-A (94%) was statistically increased compared to a historical control group (75%).

ROFERON®-A (Interferon alfa-2a, recombinant/Roche)

INDICATIONS AND USAGE: Roferon-A is indicated for use in the treatment of hairy cell leukemia in people 18 years of age or older. Studies have shown that Roferon-A can produce clinically meaningful regression or stabilization of this disease, both in previously splenectomized and nonsplenectomized patients.[2,3]
Prior to initiation of therapy, tests should be performed to quantitate peripheral blood hemoglobin, platelets, granulocytes and hairy cells and bone marrow hairy cells. These parameters should be monitored periodically (*e.g.*, monthly) during treatment to determine whether response to treatment has occurred. If a patient does not respond within six months, treatment should be discontinued. If a response to treatment does occur, treatment should be continued until no further improvement is observed and these laboratory parameters have been stable for about three months. It is not known whether continued treatment after that time is beneficial. Studies are in progress to evaluate this question.
CONTRAINDICATIONS: Roferon-A is contraindicated in patients with known hypersensitivity to alfa interferon, mouse immunoglobulin or any component of the product.
WARNINGS: Roferon-A should be administered under the guidance of a qualified physician. (See DOSAGE AND ADMINISTRATION.) Appropriate management of the therapy and its complications is possible only when adequate diagnostic and treatment facilities are readily available.
Roferon-A should be used with caution in patients with severe preexisting cardiac disease, severe renal or hepatic disease, seizure disorders and/or compromised central nervous system function.
Because of the possibility of severe or even fatal adverse reactions, patients should be informed not only of the benefits of therapy but also of the risks involved.
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-limited toxicities (*i.e.*, fever, chills) frequently associated with Roferon-A administration may exacerbate preexisting cardiac conditions. Rarely, myocardial infarction has occurred in patients receiving Roferon-A.
Caution should be exercised when administering Roferon-A to patients with myelosuppression.
Central nervous system adverse reactions have been reported in a number of patients. These reactions included decreased mental status, exaggerated central nervous system function, and dizziness. More severe obtundation and coma have been rarely observed. Most of these abnormalities were mild and reversible within a few days to three weeks upon dose reduction or discontinuation of Roferon-A therapy. Careful periodic neuropsychiatric monitoring of all patients is recommended.
Leukopenia and elevation of hepatic enzymes occurred frequently but were rarely dose-limiting. Thrombocytopenia occurred less frequently. Proteinuria and increased cells in urinary sediment were also seen infrequently. Rarely, significant hepatic, renal and myelosuppressive toxicities were noted.
PRECAUTIONS: *General:* In all instances where the use of Roferon-A is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of Roferon-A therapy should be carried out with caution and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.
The minimum effective dose of Roferon-A for treatment of hairy cell leukemia has not been established.
Information for Patient: Patients should be cautioned not to change brands of Interferon without medical consultation, as a change in dosage may result. Patients should be informed regarding the potential benefits and risks attendant to the use of Roferon-A. If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including review of the contents of the enclosed Patient Information Sheet. Patients should be well hydrated, especially during the initial stages of treatment.
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.
Since responses of hairy cell leukemia are not generally observed for one to three months after initiation of treatment, very careful monitoring for severe depression of blood cell counts is warranted during the initial phase of treatment.
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.
Carcinogenesis, Mutagenesis and Impairment of Fertility:
Carcinogenesis: Roferon-A has not been tested for its carcinogenic potential.
Mutagenesis: A. Internal studies—Ames tests using six different tester strains, with and without metabolic activation, were performed with Roferon-A up to a concentration of 1920 μg/plate. There was no evidence of mutagenicity.
Human lymphocyte cultures were treated *in vitro* with Roferon-A at noncytotoxic concentrations. No increase in the incidence of chromosomal damage was noted.
B. Published studies—There are no published studies on the mutagenic potential of Roferon-A. However, a number of studies on the genotoxicity of human leukocyte interferon have been reported.
A chromosomal defect following the addition of human leukocyte interferon to lymphocyte cultures from a patient suffering from a lymphoproliferative disorder has been reported.
In contrast, other studies have failed to detect chromosomal abnormalities following treatment of lymphocyte cultures from healthy volunteers with human leukocyte interferon.
It has also been shown that human leukocyte interferon protects primary chick embryo fibroblasts from chromosomal aberrations produced by gamma rays.
Impairment of Fertility: Roferon-A has been studied for its effect on fertility in Macaca mulatta (rhesus monkeys). Nonpregnant rhesus females treated with Roferon-A at doses of 5 and 25 million IU/kg/day have shown menstrual cycle irregularities, including prolonged or shortened menstrual periods and erratic bleeding; these cycles were considered to be anovulatory. These monkeys returned to a normal menstrual rhythm following discontinuation of treatment.
Drug Interactions: Interactions between Roferon-A and other drugs have not been fully evaluated.

PREGNANCY: *Teratogenic Effects:* Pregnancy Category C. Roferon-A has been shown to demonstrate a statistically significant increase in abortifacient activity in rhesus monkeys when given at approximately 20 to 500 times the human dose. A study in pregnant rhesus monkeys treated with 1, 5 or 25 million IU/kg/day of Roferon-A in their early to midfetal period (days 22 to 70 of gestation) has failed to demonstrate teratogenic activity for Roferon-A. There are no adequate and well-controlled studies in pregnant women.
Nonteratogenic Effects: Dose-related abortifacient activity was observed in pregnant rhesus monkeys treated with 1, 5 or 25 million IU/kg/day of Roferon-A in their early to midfetal period (days 22 to 70 of gestation). A late-fetal period study (days 79 to 100 of gestation) is in progress and as yet there have been no reports of any increased rate of abortion.
Usage in Pregnancy: Safe use in human pregnancy has not been established. Therefore, Roferon-A should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Information from primate studies showed dose-related menstrual irregularities and an increased incidence of spontaneous abortions. Therefore, fertile women should not receive Roferon-A unless they are using effective contraception during the therapy period.
Male fertility and teratologic evaluations have yielded no significant adverse effects to date.
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 from Roferon-A, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children under 18 years of age have not been established.
ADVERSE REACTIONS: The following data on adverse reactions are based on the subcutaneous or intramuscular administration of Roferon-A as a single agent for the treatment of 63 patients with hairy cell leukemia during investigational trials in the United States.
Flu-like syndromes consisting of fatigue (89%), fever (98%), chills (64%), myalgias (73%) and headache (71%) occurred in the majority of patients and tended to diminish with continuing therapy. Other side effects such as anorexia (46%), nausea (32%), emesis (10%), diarrhea (29%), dizziness (21%), rash (18%), change in taste (13%), dryness or inflammation of the oropharynx (16%), dry skin or pruritus (13%) and weight loss (14%) were observed with moderate frequency. Less commonly, diaphoresis (8%), paresthesias (6%), numbness (6%), partial alopecia (8%), reactivation of herpes labialis (8%), transient impotence (6%) and arthralgias (5%) were also observed. Rarely (<3%), central nervous system effects including decreased mental status, depression, visual disturbances, sleep disturbances and nervousness, as well as cardiac adverse events, including hypertension, chest pain, arrhythmias and palpitations, were reported. Adverse experiences which occurred rarely and may have been related to underlying disease, included epistaxis, bleeding gums, ecchymosis and petechiae. Miscellaneous adverse events, such as night sweats, urticaria, conjunctivitis and inflammation at the site of injection, were also rarely observed.
Roferon-A has also been evaluated for the treatment of many other types of cancer under investigational trials in the United States. These studies generally utilized higher doses (12 to 50 million IU/m²). All of the previously described adverse reactions which occurred in patients with hairy cell leukemia were also observed in patients receiving higher doses. The incidence of most adverse reactions was similar between the two groups, but tended to be more severe in patients who received higher doses of Roferon-A. Some additional adverse effects which occurred in these patients included confusion (10%), hypotension (6%), lethargy (3%) and edema (3%). Adverse experiences occurring in less than 1% of these patients and observed only in patients with malignancies other than hairy cell leukemia are as follows: *Gastrointestinal*—abdominal fullness, hypermotility and hepatitis; *Central Nervous System*—gait disturbance, poor coordination, hallucinations, syncope, seizures, encephalopathy, psychomotor retardation, coma, stroke, transient ischemic attacks, aphasia, aphonia, dysarthria, dysphasia, forgetfulness, amnesia, sedation, apathy, anxiety, emotional lability, irritability, hyperactivity, involuntary movements, claustrophobia and loss of libido; *Peripheral Nervous System*—muscle contractions; *Cardiovascular*—congestive heart failure, pulmonary edema, myocardial infarction, Raynaud's phenomenon and hot flashes; *Pulmonary*—bronchospasm and tachypnea; *Miscellaneous*—excessive salivation and flushing of skin.
Abnormal Laboratory Test Values: The percentage of patients with hairy cell leukemia or with other types of malignancies who experienced a significant abnormal laboratory test value at least once during their treatment is shown in the following table:

ABNORMAL LABORATORY TEST VALUES

	Hairy Cell Leukemia (n = 63)	Overall Safety Summary* (n = 1019)
Hematologic		
Leukopenia	59%	69%
Neutropenia	39%	58%
Thrombocytopenia	42%	42%
Decreased Hemoglobin	36%	6.3%
Decreased Hematocrit	43%	12.5%
Mean Time to Nadir		
WBC	38 days	22 days
Platelets	19 days	17 days
Hepatic		
SGOT	47%	78%
Alkaline Phosphatase	18%	48%
LDH	12%	47%
Bilirubin	1.6%	31%
Renal/Urinary		
BUN	2%	10%
Serum Creatinine	3%	10%
Uric Acid†	6%	15%
Proteinuria†	10%	25%
Other Chemistry Tests		
Hypocalcemia	10%	51%
Elevated FBS‡	33%	39%
Elevated Serum Phosphorus	2%	17%

ROFERON®-A (interferon alfa-2a, recombinant/Roche)

*Patients with hairy cell leukemia are included in this overall summary.
†The majority of abnormal uric acid values and proteinuria were of minimal severity. Since these abnormalities are commonly observed in patients with advanced malignancy, it is difficult to ascertain their relationship to Roferon-A treatment.
‡Random glucose determination.

Neutralizing antibodies to Roferon-A were detected in approximately 27% of all patients (3.4% for patients with hairy cell leukemia). No clinical sequelae of their presence have been documented thus far. 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.[4]
DOSAGE AND ADMINISTRATION: Hairy Cell Leukemia—The induction dose of Roferon-A is 3 million IU daily for 16 to 24 weeks, administered as a subcutaneous or intramuscular injection. Subcutaneous administration is particularly advisable for, but not limited to, thrombocytopenic patients (platelet count <50,000) or for patients at risk for bleeding. The recommended maintenance dose is 3 million IU, three times per week. Dosage reduction by one-half or withholding of individual doses may be needed when severe adverse reactions occur. The use of doses higher than 3 million IU is not recommended.
Patients should be treated for approximately six months before the physician determines whether to continue therapy in patients who respond or discontinue therapy in patients who did not respond. Patients with hairy cell leukemia have been treated for up to 20 consecutive months. The optimal duration of treatment for this disease has not been determined.
If severe reactions occur, dosage should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. The need for dosage reduction should take into account the effects of prior X-ray therapy or chemotherapy that may have compromised bone marrow reserve. The minimum effective dose of Roferon-A has not been established.
DIRECTIONS FOR USE: 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.
Injectable Solution:
3 million IU Roferon-A per vial—Each 1 mL contains 3 million IU of Interferon alfa-2a, recombinant/Roche, 9 mg sodium chloride for isotonicity, 5 mg human serum albumin as a stabilizer and 3 mg phenol as a preservative.
18 million IU Roferon-A per vial (for multiple-dose use)—Each 1 mL contains 6 million IU of Interferon alfa-2a, recombinant/Roche, 9 mg sodium chloride for isotonicity, 5 mg human serum albumin as a stabilizer and 3 mg phenol as a preservative. Each 0.5 mL contains 3 million IU of Interferon alfa-2a, recombinant/Roche.
The injectable solution should be stored in the refrigerator at 36° to 46°F (2° to 8°C). Do *not* freeze. Do not shake.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
HOW SUPPLIED: Sterile Roferon-A is supplied as single and multiple-dose vials:
Roferon-A Injectable Solution: Vials containing 3 million IU Interferon alfa-2a, recombinant/Roche (3 million IU/mL). Boxes of 10 (NDC 0004-1987-01).
Roferon-A Injectable Solution: Multiple-dose vials containing 18 million IU Interferon alfa-2a, recombinant/Roche (3 million IU/0.5 mL). Boxes of 1 (NDC 0004-1988-09).
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4. Jones GJ, Itri LM: *Cancer 57*(Suppl.):1709-1715, 1986.

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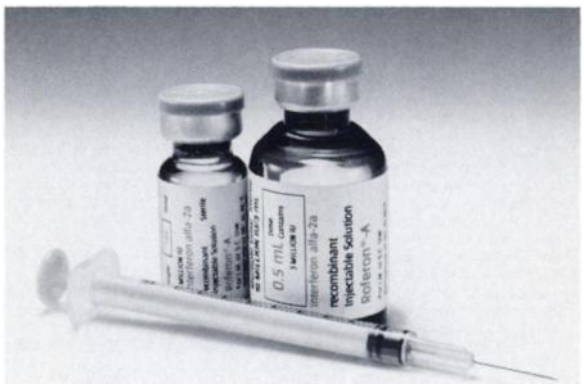

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