



ROFERON®-A

(Interferon alfa-2a, recombinant)

Alpha interferons, including Interferon alfa-2a, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping Interferon alfa-2a therapy (see WARNINGS and ADVERSE REACTIONS).

DESCRIPTION: Roferon-A (Interferon alfa-2a, recombinant) is a sterile protein product for use by injection. Roferon-A is manufactured by recombinant DNA technology that employs a genetically engineered *Escherichia coli* bacterium containing DNA that codes for the human protein. Interferon alfa-2a, recombinant is a highly purified protein containing 165 amino acids, and it has an approximate molecular weight of 19,000 daltons. Fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride, 5 mg/L. However, the presence of the antibiotic is not detectable in the final product. Roferon-A is supplied as an injectable solution in a vial or a prefilled syringe. Each glass syringe barrel contains 0.5 mL of product. In addition, there is a needle which is 1/2 inch in length.

Single Use Injectable Solution:

36 million IU (133.3 mcg/mL) Roferon-A per vial — The solution is colorless and each mL contains 36 MIU of Interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate.

Single Use Prefilled Syringes:

3 million IU (111 mcg/0.5 mL) Roferon-A per syringe — The solution is colorless and each 0.5 mL contains 3 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

6 million IU (22.2 mcg/0.5 mL) Roferon-A per syringe — The solution is colorless and each 0.5 mL contains 6 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

9 million IU (33.3 mcg/0.5 mL) Roferon-A per syringe — The solution is colorless and each 0.5 mL contains 9 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

Multidose Injectable Solution:

18 million IU (66.7 mcg/3 mL) Roferon-A per vial — The solution is colorless and each mL contains 6 MIU of Interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate. Each 0.5 mL contains 3 MIU of Interferon alfa-2a, recombinant.

Based on the specific activity of 2.7x10¹⁰IU/mg protein, the corresponding quantities of Interferon alfa-2a, recombinant in the vials described above are approximately 18 MIU (66.7 mcg/3 mL) and 36 MIU (133.3 mcg/mL).

The route of administration for the vial is subcutaneous or intramuscular; the route of administration for the prefilled syringe is subcutaneous only.

CLINICAL PHARMACOLOGY: The mechanism by which Interferon alfa-2a, recombinant, or any other interferon, exerts antitumor or antiviral activity is not clearly understood. However, it is believed that direct antiproliferative action against tumor cells, inhibition of virus replication and modulation of the host immune response play important roles in antitumor and antiviral activity.

The biological activities of Interferon alfa-2a, recombinant are species-restricted, ie, they are expressed in a very limited number of species other than humans. As a consequence, preclinical evaluation of Interferon alfa-2a, recombinant has involved in vitro experiments with human cells and some in vivo experiments: Using human cells in culture, Interferon alfa-2a, recombinant 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 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 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 appear in the urine of isolated rat kidneys, suggesting near complete reabsorption of Interferon alfa-2a, recombinant catabolites. Liver metabolism and subsequent biliary excretion are considered minor pathways of elimination for alfa interferons.

The serum concentrations of Interferon alfa-2a, recombinant reflected a large intersubject variation in both healthy volunteers and patients with disseminated cancer.

In healthy people, Interferon alfa-2a, recombinant 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

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2.14 to 3.62 mL/min/kg (mean 2.79 mL/min/kg) after a 36 MIU (2.2x10¹⁰pg) intravenous infusion. After intramuscular and subcutaneous administrations of 36 MIU, peak serum concentrations ranged from 1500 to 2580 pg/mL (mean 2020 pg/mL) at a mean time to peak of 3.8 hours and from 1250 to 2320 pg/mL (mean 1730 pg/mL) at a mean time to peak of 7.3 hours, respectively. The apparent fraction of the dose absorbed after intramuscular injection was greater than 80%.

The pharmacokinetics of Interferon alfa-2a, recombinant 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 MIU. There were no changes in the distribution or elimination of Interferon alfa-2a, recombinant during twice daily (0.5 to 36 MIU), once daily (1 to 54 MIU), or three times weekly (1 to 136 MIU) dosing regimens up to 28 days of dosing. Multiple intramuscular doses of Interferon alfa-2a, recombinant resulted in an accumulation of two to four times the single dose serum concentrations. There is no pharmacokinetic information in patients with chronic hepatitis C, hairy cell leukemia, AIDS-related Kaposi's sarcoma and chronic myelogenous leukemia.

Serum neutralizing activity, determined by a highly sensitive enzyme immunoassay, and a neutralization bioassay, was detected in approximately 25% of all patients who received Roferon-A.² 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.³ The significance of the appearance of serum neutralizing activity is not known.

CLINICAL STUDIES: Studies have shown that Roferon-A can normalize serum ALT, improve liver histology and reduce viral load in patients with chronic hepatitis C. Other studies have shown that Roferon-A can produce clinically meaningful tumor regression or disease stabilization in patients with hairy cell leukemia or in patients with AIDS-related Kaposi's sarcoma.⁴⁻⁶ In Ph-positive Chronic Myelogenous Leukemia, Roferon-A supplemented with intermittent chemotherapy has been shown to prolong overall survival and to delay disease progression compared to patients treated with chemotherapy alone.⁷ In addition, Roferon-A has been shown to produce sustained complete cytogenetic responses in a small subset of patients with CML in chronic phase. The activity of Roferon-A in Ph-negative CML has not been determined.

EFFECTS ON CHRONIC HEPATITIS C: The safety and efficacy of Roferon-A was evaluated in multiple clinical trials involving over 2000 patients 18 years of age or older with hepatitis, with or without cirrhosis, who had elevated serum alanine aminotransferase (ALT) levels and tested positive for antibody to hepatitis C. Roferon-A was given three times a week (tw) by subcutaneous (SC) or intramuscular (IM) injection in a variety of dosing regimens, including dose escalation and de-escalation regimens. Normalization of serum ALT was defined in all studies as two consecutive normal serum ALT values at least 21 days apart. A sustained response (SR) was defined as normalization of ALT both at the end of treatment and at the end of at least 6 months of treatment-free follow-up.

In trials in which Roferon-A was administered for 6 months, 6 MIU, 3 MIU, and 1 MIU were directly compared. Six MIU was associated with higher SR rates but greater toxicity (see ADVERSE REACTIONS). In studies in which the same dose of Roferon-A was administered for 6 or 12 months, the longer duration was associated with higher SR rates and adverse events were no more severe or frequent in the second 6 months than in the first 6 months. Based on these data, the recommended regimens are 3 MIU for 12 months or 6 MIU for the first 3 months followed by 3 MIU for the next 9 months (see Table 1 and DOSAGE AND ADMINISTRATION). There are no direct comparisons of these two regimens.

Younger patients (eg, less than 35 years of age) and patients without cirrhosis on liver biopsy were more likely to respond completely to Roferon-A than those patients greater than 35 years of age or patients with cirrhosis on liver biopsy.

In the two studies in which Roferon-A was administered subcutaneously three times weekly for 12 months, 20/173 (12%) patients experienced a sustained response to therapy (see Table 1). Of these patients, 15/173 (9%) maintained this sustained response during continuous follow-up for up to four years. Patients who have ALT normalization but who fail to have a sustained response following an initial course of therapy may benefit from retreatment with higher doses of Roferon-A (see DOSAGE AND ADMINISTRATION).

A subset of patients had liver biopsies performed both before and after treatment with Roferon-A. An improvement in liver histology as assessed by Knodell Histology Activity Index was generally observed.

A retrospective subgroup analysis of 317 patients from two studies suggested a correlation between improvement in liver histology, durable serum ALT response rates, and decreased viral load as measured by the polymerase chain reaction (PCR).

Study No.	Dose (MIU)	N	End of Treatment [% (95% CI)]	End of Observation (Sustained Response SR) [% (95% CI)]*
1**	3	56	23	11
2	3	117	23	12
1 and 2 Combined	3	173	23 (17-30)	12 (7-17)
3	6-3	210	25 (19-31)	19 (14-25)

* All patients were followed for 6 months after end of treatment.

**EOT and SR rates for Placebo (study 1) were 0.

EFFECTS ON Ph-POSITIVE CHRONIC MYELOGENOUS LEUKEMIA (CML): Roferon-A was evaluated in two trials of patients with chronic phase CML. Study DM84-38 was a single center phase II study conducted at the MD Anderson Cancer Center, which enrolled 91 patients, 81% were previously treated, 82% were Ph positive, and 63% received Roferon-A within 1 year of diagnosis. Study MI400 was a multicenter randomized phase III study conducted in Italy by the Italian Cooperative Study Group on CML in 335 patients; 226 Roferon-A and 109 chemotherapy. Patients with Ph-positive, newly diagnosed or minimally treated CML were randomized (ratio 2:1) to either Roferon-A or conventional chemotherapy with either hydroxyurea or busulfan. In study DM84-38, patients started Roferon-A at 9 MIU/day, whereas in study MI400, it was progressively escalated from 3 to 9 MIU/day over the first month. In both trials, dose escalation for insufficient hematologic response, and dose attenuation or interruption for toxicity was permitted. No formal guidelines for dose attenuation were given in the chemotherapy arm

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of study MI400. In addition, in the Roferon-A arm, the MI400 protocol allowed the addition of intermittent single agent chemotherapy for insufficient hematologic response to Roferon-A alone. In this trial, 44% of the Roferon-A treated patients also received intermittent single agent chemotherapy at some time during the study.

The two studies were analyzed according to uniform response criteria. For hematologic response: complete response (WBC <9x10⁹/L, normalization of the differential with no immature forms in the peripheral blood, disappearance of splenomegaly), partial response (>50% decrease from baseline of WBC to <20%x10⁹/L). For cytogenetic response: complete response (0% Ph-positive metaphases), partial response (1% to 34% Ph-positive metaphases).

In study DM84-38, the median survival from initiation of Roferon-A was 47 months. In study MI400, the median survival for the patients on the interferon arm was 69 months, which was significantly better than the 55 months seen in the chemotherapy control group (48 patients in study MI400 proceeded to BMT and in study DM84-38, 15 patients proceeded to BMT). Roferon-A treatment significantly delayed disease progression to blastic phase as evidenced by a median time to disease progression of 69 months to 46 months with chemotherapy.

By multivariate analysis of prognostic factors associated with all 335 patients entered into the randomized study, treatment with Roferon-A (with or without intermittent additional chemotherapy; p=0.006), Sokal index⁸ (p=0.006) and WBC (p=0.023) were the three variables associated with an improved survival, independent of other baseline characteristics (Karnofsky performance status and hemoglobin being the other factors entered into the model).

In study MI400, overall hematologic responses, [complete responses (CR) and partial responses (PR)], were observed in approximately 60% of patients treated with Roferon-A (40% CR, 20% PR), compared to 70% with chemotherapy (30% CR, 40% PR). The median time to reach a complete hematologic response was 5 months in the Roferon-A arm and 4 months in the chemotherapy arm. The overall cytogenetic response rate (CR+PR), in patients receiving Roferon-A, was 10% and 12% in studies MI400 and DM84-38, respectively, according to the intent-to-treat principle. In contrast, only 2% of the patients in the chemotherapy arm of study MI400 achieved a cytogenetic response (with no complete responses). Cytogenetic responses were observed only in patients who had complete hematologic responses. In study DM84-38, hematologic and cytogenetic response rates were higher in the subset of patients treated with Roferon-A within 1 year of diagnosis (76% and 17%, respectively) compared to the subset initiating Roferon-A therapy more than 1 year from diagnosis (29% and 4%, respectively). In an exploratory analysis, patients who achieved a cytogenetic response lived longer than those who did not.

Severe adverse events were observed in 66% and 31% of patients on study DM84-38 and MI400, respectively. Dose reduction and temporary cessation of therapy was required frequently. Permanent cessation of Roferon-A, due to intolerable side effects, was required in 15% and 23% of patients on studies DM84-38 and MI400, respectively (see ADVERSE REACTIONS).

Limited data are available on the use of Roferon-A in children with Ph-positive, adult-type CML. A published report on 15 children with CML suggests a safety profile similar to that seen in adult CML; clinical responses were also observed⁹ (see DOSAGE AND ADMINISTRATION).

EFFECTS ON HAIRY CELL LEUKEMIA: A multicenter US phase II study (N2752) enrolled 218 patients; 75 were evaluable for efficacy in a preliminary analysis; 218 patients were evaluable for safety. Patients were to receive a starting dose of Roferon-A up to 6 MIU/m²/day, for an induction period of 4 to 6 months. Responding patients were to receive 12 months maintenance therapy.

During the first 1 to 2 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, 8 (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 2 years in patients receiving Roferon-A (94%) was statistically increased compared to a historical control group (75%).

EFFECTS ON AIDS-RELATED KAPOSI'S SARCOMA: In six studies with Roferon-A, doses of 3 to 54 MIU daily were evaluated for the treatment of AIDS-related Kaposi's sarcoma in more than 350 patients. Four dosage regimens of Roferon-A were evaluated for initial induction. Thirty-nine patients received 3 MIU daily; 99 patients received an escalating regimen of 3 MIU, 9 MIU and 18 MIU each daily for 3 days, followed by 36 MIU daily; 119 patients received 36 MIU daily; and 16 patients received doses greater than 36 MIU to a maximum of 54 MIU daily. An additional 91 patients received Roferon-A in combination with vinblastine. The best response rate associated with acceptable toxicity was observed when Roferon-A was administered as a single agent at a dose of 36 MIU daily. The escalating regimen of 3 to 36 MIU daily provided equivalent therapeutic benefit with some amelioration of acute toxicity in some patients. In AIDS-related Kaposi's sarcoma, lower doses were less effective in inducing tumor regression and doses higher than 36 MIU daily were associated with unacceptable toxicity.

As summarized in Table 2, the likelihood of response to Roferon-A varied with the clinical manifestations of human immunodeficiency virus (HIV) infection. Patients with prior opportunistic infection or B symptoms are unlikely to respond to treatment with Roferon-A.

No. Pts. *	CD ₄ (T ₄) Lymphocyte Count (cells/mm ³)	Objective Response Rate (%)		
		CR	PR	Total
83	0-200	3.6	3.6	7.2
51	201-400	15.7	11.8	27.5
33	>400	24.2	21.2	45.4

In the 28 patients evaluated who had prior opportunistic infection or B symptoms, the response rate was 3.6%.

*Patients had no prior opportunistic infection or B symptoms. B symptoms include night sweats, weight loss of greater than 10% of body weight or 15 lbs, or fever greater than 100°F without an identifiable source of infection.

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Patients who were otherwise asymptomatic, with no prior opportunistic infection and near-normal levels of CD₄ lymphocytes, experienced higher response rates. Responding patients with a baseline CD₄ lymphocyte count greater than 200 cells/mm³ had a distinct survival advantage over both responding patients with a baseline CD₄ lymphocyte count of 200 cells/mm³ or less and non-responding patients regardless of their baseline CD₄ lymphocyte count. Median survival for responding patients with CD₄ lymphocyte counts of greater than 200 to 400 cells/mm³ had not been reached but was greater than 32.7 months from the initiation of therapy. For responding patients with CD₄ lymphocyte counts of greater than 400 cells/mm³, the median survival had not been reached but was greater than 29.5 months.

A classification system for staging AIDS-related Kaposi's sarcoma has been described based on location and extent of disease. In studies of Roferon-A, no difference was noted in response rates for patients with different stages of Kaposi's sarcoma. Likelihood of response was related to manifestations of HIV infection (baseline CD₄ lymphocyte count, prior opportunistic infection or B symptoms) and not to extent of tumor involvement. The median time to response was 2.7 months. The median duration of response for patients achieving a partial or complete response was 6.3 and 20.7 months, respectively. Complete and partial responses lasting in excess of 3 years have been observed. Therapy was discontinued because of progression of Kaposi's sarcoma, development of severe opportunistic infection or severe adverse effects. The median time to discontinuation of treatment was 12.5 months for responding patients and 2.3 months for patients who did not respond.

INDICATIONS AND USAGE: Roferon-A is indicated for the treatment of chronic hepatitis C, hairy cell leukemia and AIDS-related Kaposi's sarcoma in patients 18 years of age or older. In addition, it is indicated for chronic phase, Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis).

FOR PATIENTS WITH CHRONIC HEPATITIS C: Roferon-A is indicated for use in patients with chronic hepatitis C diagnosed by HCV antibody and/or a history of exposure to hepatitis C who have compensated liver disease and are 18 years of age or older. A liver biopsy and a serum test for the presence of antibody to HCV should be performed to establish the diagnosis of chronic hepatitis C. Other causes of hepatitis, including hepatitis B, should be excluded prior to therapy with Roferon-A.

FOR PATIENTS WITH AIDS-RELATED KAPOSI'S SARCOMA: Roferon-A is indicated for the treatment of AIDS-related Kaposi's sarcoma in a select group of patients. In determining whether a patient should be treated, the physician should assess the likelihood of response based on the clinical manifestations of HIV infection, including prior opportunistic infections, presence of B symptoms, and CD₄ count, and the manifestations of Kaposi's sarcoma requiring treatment (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS: Roferon-A is contraindicated in patients with known hypersensitivity to alfa interferon or any component of the product. The injectable solutions contain benzyl alcohol and are contraindicated in any individual with a known allergy to that preservative.

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 facilities are readily available.

DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL IDEATION, SUICIDAL ATTEMPTS AND SUICIDES HAVE BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALFA INTERFERONS, INCLUDING ROFERON-A. Patients to be treated with Roferon-A should be informed that depression and suicidal ideation may be side effects of treatment and should be advised to report these side effects immediately to the prescribing physician. Patients receiving Roferon-A therapy should receive close monitoring for the occurrence of depressive symptomatology. Cessation of treatment should be considered for patients experiencing depression. Although dose reduction or treatment cessation may lead to resolution of the depressive symptomatology, depression may persist and suicides have occurred after withdrawing therapy (see PRECAUTIONS and ADVERSE REACTIONS).

Central nervous system adverse reactions have been reported in a number of patients. These reactions included decreased mental status, dizziness, impaired memory, agitation, manic behavior and psychotic reactions. More severe obtundation and coma have been rarely observed. Most of these abnormalities were mild and reversible within a few days to 3 weeks upon dose reduction or discontinuation of Roferon-A therapy. Careful periodic neuropsychiatric monitoring of all patients is recommended.

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.

Roferon-A should be administered with caution to patients with cardiac disease or with any history of cardiac illness. Acute, self-limited toxicities (ie, fever, chills) frequently associated with Roferon-A administration may exacerbate preexisting cardiac conditions. Rarely, myocardial infarction has occurred in patients receiving Roferon-A. Cases of cardiomyopathy have been observed on rare occasions in patients treated with alfa interferons.

Patients with a history of autoimmune hepatitis or a history of autoimmune disease and patients who are immunosuppressed transplant recipients should not be treated with Roferon-A. Controlled studies of Roferon-A therapy in patients with advanced cirrhosis and/or decompensated liver disease have not been performed. In chronic hepatitis C, initiation of alfa-interferon therapy, including Roferon-A, has been reported to cause transient liver abnormalities, which in patients with poorly compensated liver disease can result in increased ascites, hepatic failure or death.

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. Dose-limiting hepatic or renal toxicities were unusual. Infrequently, severe renal toxicities, sometimes requiring renal dialysis, have been reported with alfa-interferon therapy alone or in combination with IL-2 (see PRECAUTIONS).

Infrequently, severe or fatal gastrointestinal hemorrhage has been reported in association with alfa-interferon therapy.

Alpha interferons suppress bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pretreatment and monitored routinely during therapy. Alpha interferon therapy should be discontinued in patients who develop severe decreases in neutrophil (<0.5 x 10⁹/L) or platelet counts (<25 x 10⁹/L).

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Caution should be exercised when administering Roferon-A to patients with myelosuppression or 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).³ The effects of Roferon-A when combined with other drugs used in the treatment of AIDS-related disease are not known.

Hyperglycemia has been observed rarely in patients treated with Roferon-A. Symptomatic patients should have their blood glucose measured and followed-up accordingly. Patients with diabetes mellitus may require adjustment of their anti-diabetic regimen.

Roferon-A should not be used for the treatment of visceral AIDS-related Kaposi's sarcoma associated with rapidly progressive or life-threatening disease.

The injectable solutions contain benzyl alcohol and should not be used by patients with a known allergy to benzyl alcohol. This product is not indicated for use in neonates or infants and should not be used by patients in that age group. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. There have been reports of permanent neuropsychiatric deficits and multiple system organ failure associated with benzyl alcohol in neonates and infants. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known (see CONTRAINDICATIONS).

Ophthalmologic Disorders: Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema are induced or aggravated by treatment with Interferon alfa-2a or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Interferon alfa-2a treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

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 to possible recurrence of toxicity. The minimum effective doses of Roferon-A for treatment of hairy cell leukemia, AIDS-related Kaposi's sarcoma and chronic myelogenous leukemia have not been established.

Variations in dosage and adverse reactions exist among different brands of Interferon. Therefore, do not use different brands of Interferon in a single treatment regimen.

Rare cases of autoimmune diseases including thrombocytopenia, vasculitis, Raynaud's phenomenon, rheumatoid arthritis, lupus erythematosus, and rhabdomyolysis have been observed in patients treated with alpha interferons. Any patient developing an autoimmune disorder during treatment should be closely monitored and, if appropriate, treatment should be discontinued.

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.

Patients should be thoroughly instructed in the importance of proper disposal procedures and cautioned against reusing syringes and needles. If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. The full container should be disposed of according to directions provided by the physician.

Patients receiving high-dose alfa interferon should be cautioned against performing tasks that require complete mental alertness such as operating machinery or driving a motor vehicle. Patients to be treated with Roferon-A should be informed that depression and suicidal ideation may be side effects of treatment and should be advised to report these side effects immediately to the prescribing physician.

Laboratory Tests: Complete blood with differential platelet counts and clinical chemistry tests should be performed before initiation of Roferon-A therapy and at appropriate periods during therapy. Since responses of hairy cell leukemia, AIDS-related Kaposi's sarcoma, chronic hepatitis C and chronic myelogenous leukemia are not generally observed for 1 to 3 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 before and during the course of treatment.

For patients being treated for chronic hepatitis C, serum ALT should be evaluated before therapy to establish baselines and repeated at week 2 and monthly thereafter following initiation of therapy for monitoring clinical response. Patients with neutrophil count <1500/mm³, platelet count <75,000/mm³, hemoglobin <10 g/dL and creatinine >1.5 mg/dL were excluded from several major chronic hepatitis C studies; patients with these laboratory abnormalities should be carefully monitored if treated with Roferon-A.

Patients with preexisting thyroid abnormalities may be treated if normal thyroid stimulating hormone (TSH) levels can be maintained by medication. Testing of TSH levels in these patients is recommended at baseline and every 3 months following initiation of therapy.

Drug Interactions: Roferon-A has been reported to reduce the clearance of theophylline.^{11,12} The clinical relevance of this interaction is presently unknown. Interactions between Roferon-A and other drugs have not been fully evaluated. Caution should be exercised when administering Roferon-A in combination with other potentially myelosuppressive agents (see WARNINGS).

Other Drug Interactions: Alfa interferons may affect the oxidative metabolic process by reducing the activity of hepatic 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.

