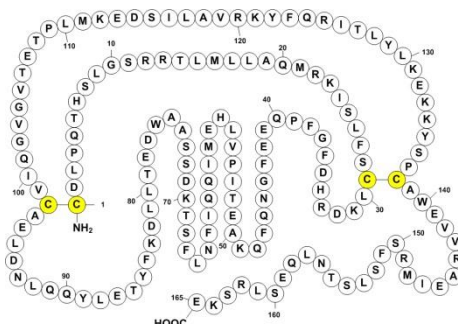


## NAME OF THE MEDICINE

### ROFERON-A®

*interferon alfa-2a*

CAS-76543-88-9



## DESCRIPTION

Roferon-A (interferon alfa-2a) is a sterile protein product for use by injection. ROFERON-A is produced biosynthetically using recombinant DNA technology, and is the product of a cloned human leucocyte interferon gene inserted into and expressed in *E.coli*. Interferon alfa-2a is a highly purified protein containing 165 amino acids. It has an approximate molecular weight of 19 kD.

Roferon-A solution for injection is supplied as pre-filled syringes containing interferon alfa-2a, sodium chloride, ammonium acetate, benzyl alcohol, polysorbate 80, glacial acetic acid, sodium hydroxide and water for injections. 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.

Each pre-filled syringe of Roferon-A solution for injection contains 3 or 9 million international units (MIU) of interferon alfa-2a. The specific activity of interferon alfa-2a is approximately 270 MIU/mg protein. Roferon-A should be administered by subcutaneous injection.

## PHARMACOLOGY

### PHARMACODYNAMICS

*Mechanism of action:* The mechanism by which interferon alfa-2a, or any other interferon, exerts anti-tumour activity is not clearly understood. However, it is believed that direct anti-proliferative action against tumour cells and modulation of the host immune response play important roles in the anti-tumour activity.

Roferon-A exerts its antiviral effects by inducing a state of resistance to viral infections in cells and by modulating the effector arm of the immune system to neutralise viruses or eliminate virus-infected cells.

The biological activities of interferon alfa-2a 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 has involved *in vitro* experiments with human cells and some *in vivo* experiments. Using human cells in culture, interferon alfa-2a has been shown to have anti-proliferative and immunomodulatory activities that are very similar to those of the mixture of interferon alfa subtypes produced by human leucocytes. *In vivo*, interferon alfa-2a has been shown to inhibit the growth of several human tumours growing in immunocompromised (nude) mice. Because of its species-restricted activity, it has not been possible to demonstrate anti-tumour activity in immunologically intact syngeneic tumour model systems, where effects on the host immune system would be observable. However, such anti-tumour activity has been repeatedly demonstrated with, for example, mouse interferon alfa in transplantable mouse tumour systems. The clinical significance of these findings is unknown.

In a pharmacological study in 9 subjects, ROFERON-A was shown to inhibit hepatic oxidative drug metabolism as measured by anti-pyrine clearance.

## PHARMACOKINETICS

**Absorption:** The serum concentrations of interferon alfa-2a reflected a large intersubject variation in both healthy volunteers and patients with disseminated cancer. After intramuscular (IM) and subcutaneous (SC) administrations of 36 MIU, peak serum concentrations ranged from 1500 – 2580 pg/mL (mean 2020 pg/mL) at a mean time to peak of 3.8 h and from 1250 – 2320 pg/mL (mean 1730 pg/mL) at a mean time peak of 7.3 h, respectively. The apparent fraction of the dose absorbed after IM injection was greater than 80%. Multiple IM doses of interferon alfa-2a resulted in an accumulation of 2 – 4 times the single dose serum concentrations.

**Distribution:** In healthy people, interferon alfa-2a exhibited a volume of distribution at steady-state of 0.223 – 0.748 L/kg (mean 0.400 L/kg) after a 36 MIU ( $2.2 \times 10^8$  pg) intravenous (IV) infusion. Small amounts of radiolabelled interferon alfa-2a appear in the urine of isolated rat kidneys, suggesting near complete reabsorption of interferon alfa-2a catabolites.

**Metabolism:** The metabolism of interferon alfa-2a 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.

**Elimination:** Renal catabolism is the major pathway for Roferon-A elimination. Liver metabolism and subsequent biliary excretion are considered minor pathways of elimination of ROFERON-A. In healthy people, interferon alfa-2a exhibited an elimination half-life of 3.7 – 8.5 h (mean 5.1 h) and a total body clearance of 2.14 – 3.62 mL/min/kg (mean 2.79 mL/min/kg) after a 36 MIU ( $2.2 \times 10^8$  pg) IV infusion. Theophylline clearance has also been measured before and during interferon administration. Clearance decreased from 190 mL/min to 45 mL/min and correspondingly the elimination half-life increased from 4.7 h to 11.6 h.

**Pharmacokinetics in Special Populations:** The pharmacokinetics of interferon alfa-2a after single IM doses to patients with disseminated cancer and chronic active hepatitis B 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 during twice daily (0.5 – 36 MIU), once daily (1 – 54 MIU), or three times a week (1 – 136 MIU) dosing regimens up to 28 days of dosing.

Pharmacokinetic information in patients with hairy cell leukaemia or AIDS-related Kaposi's sarcoma is presently unknown.

The acute parenteral toxicity of interferon alfa-2a has been studied in mice, rats, rabbits and ferrets at doses up to 30 MIU/kg IV, and 500 MIU/kg IM. No treatment-related mortality was noted in any species given interferon alfa-2a by any of the routes of administration.

*Anti-Interferon Antibodies:* Neutralising antibodies to proteins may be formed in some subjects following homologous administration. Antibodies to all interferons, whether natural or recombinant, are therefore likely to be found in a certain proportion of patients. In certain clinical conditions (cancer, systemic lupus erythematosus, herpes zoster), antibodies to human leucocyte interferon may also occur spontaneously in patients who have never received exogenous interferon.

In clinical trials where Roferon-A which had been stored at 25°C was used, neutralising antibodies to Roferon-A have been detected in approximately one fifth of patients. The significance of the appearance of serum neutralising antibodies on pharmacokinetics and efficacy is unclear. In most cases there appears to be no effect on efficacy. However, in a small proportion of cases loss of efficacy has been associated with detection of neutralising activity. In patients with hepatitis C, a trend for responding patients who develop neutralising antibodies to lose response while still on treatment and to lose it earlier than patients, who do not develop such antibodies, has been seen. No other clinical sequelae of the presence of antibodies to ROFERON-A have been documented.

## **CLINICAL TRIALS**

Studies have shown that Roferon-A can produce clinically meaningful regression or stabilisation of hairy cell leukaemia both in previously splenectomised and nonsplenectomised patients and can induce clinical responses in patients with advanced renal cell carcinoma (RCC), AIDS-related Kaposi's sarcoma, chronic active hepatitis B, chronic hepatitis C, chronic myelogenous leukaemia and cutaneous T-cell lymphoma. Studies have also shown that ROFERON-A prolongs the time to relapse in patients with low-grade non-Hodgkin's lymphoma when used as an adjunct to or concomitant with chemotherapy (with or without radiotherapy).

### **Chronic Hepatitis C**

#### **Roferon-A Monotherapy**

ROFERON-A has been shown to produce a decrease in biochemical markers maintained after completion of treatment in chronic active hepatitis C. However the percentage of cases with biochemical response maintained after completion of treatment varied markedly between studies. Histological indices of liver inflammation and detection of hepatitis C virus also decrease in a significant number of cases.

## ROFERON-A Combination Therapy

*Previously Untreated Patients:* A randomised, controlled trial was conducted to investigate the sustained efficacy of combining ROFERON-A with ribavirin compared to ROFERON-A alone. Sixty non-cirrhotic patients with chronic hepatitis C participated in this trial for 24 weeks treatment with a 72 week treatment-free follow-up period. Patients were followed up at 4 week intervals for the initial 24 weeks and every 8 weeks thereafter for a total of 96 weeks.

Patients were randomised to one of three treatment regimens: 21 patients received ROFERON-A 3 MIU subcutaneous (SC) three times a week with ribavirin 1200 mg daily; 19 patients received ROFERON-A 3 MIU SC; and 20 patients received no treatment.

Virological response, defined as negative HCV-RNA (determined by Polymerase Chain Reaction using the COBAS-AMPLICOR® version 2.0, sensitivity to 100 copies/mL) was measured at the end of treatment and during the follow-up period to determine sustained virological response (see Table 1).

Virological response was reported more frequently in those patients treated with ROFERON-A with ribavirin combination therapy than those treated with ROFERON-A alone. Patients receiving ROFERON-A with ribavirin combination therapy maintained a significantly higher rate of sustained virological response for up to 2 years.

**Table 1. Virological Responses\***

	<b>ROFERON-A + Ribavirin n = 21</b>	<b>ROFERON-A n = 19</b>	<b>p-value (Fisher's Exact Test)</b>
Sustained Virological Response (week 48)	48%	11%	0.016
Sustained Virological Response (week 72)	43%	6 %	0.009
Sustained Virological Response (week 96)	43%	6 %	0.009
Virological Response, End of treatment (week 24)	90%	42%	0.002

\*Intent to treat population

Histological response was measured in 28 out of 60 patients by the Knodell Histology Activity Index (HAI). Histological improvements were defined as a decrease in the inflammation score of at least 2 points. Histology changes indicated that there was no significant difference between treatment groups.

*Relapsed Patients:* ROFERON-A in combination with ribavirin has been investigated in chronic hepatitis C patients who had relapsed after treatment with interferon alfa monotherapy. In a placebo controlled, double-blind trial 99 patients were randomised into two treatment groups; 49 patients received ROFERON-A 4.5 MIU SC three times a week with ribavirin 1000 mg daily in two divided doses and 50 patients received ROFERON-A 4.5 MIU SC three times a week with placebo. The treatment duration was 24 weeks with a 24 week treatment-free follow-up period.

Virological response, as defined for previously untreated patients, was measured at the end of treatment and during the treatment-free follow-up period to determine sustained response (see Table 2).

Sustained responses were significantly higher for ROFERON-A with ribavirin combination treated patients compared to ROFERON-A with placebo.

**Table 2. Virological Responses\***

	<b>ROFERON-A with ribavirin <i>n</i> = 49</b>	<b>ROFERON-A with placebo <i>n</i> = 50</b>	<b><i>p</i>-value (Fisher's exact test)</b>
Sustained Virological Response (week 48) All Genotypes	43% (21/49)	4% (2/50)	<i>p</i> < 0.01
Sustained Virological Response (week 48) Genotype 1	28% (7/25)	0% (0/24)	<i>p</i> < 0.01
Sustained Virological Response (week 48) Genotype non-1	28% (14/24)	8% (2/26)	<i>p</i> < 0.01
Virological Response (week 24) All Genotypes	88% (43/49)	46% (23/50)	<i>p</i> < 0.01

\*Intent to treat population

Liver biopsies were conducted post-treatment to determine any improvements in histology. Histological improvements were defined as a decrease in the inflammation score of at least 2 points using the Knodell HAI (see Table 3). Fibrosis was graded according to the Metavir system in which a score of 0 indicated the absence of fibrosis and a score of 4 the presence of cirrhosis. Fibrosis was usually moderate, mild or absent in patients treated with ROFERON-A with ribavirin combination therapy but usually severe, moderate or mild in patients treated with ROFERON-A alone.

**Table 3. Overall Histological Response**

	<b>ROFERON-A with ribavirin <i>n</i> = 38</b>	<b>ROFERON-A with placebo <i>n</i> = 42</b>	<b><i>p</i>-value (Wilcoxon test)</b>
Knodell HAI*			
Improvement	68%	45%	<i>p</i> = 0.03
Stabilisation	18%	29%	
Deterioration	13%	26%	
Metavir fibrosis score			
F0	8%	0%	<i>p</i> < 0.05
F1	61%	49%	
F2	26%	37%	
F3	3%	12%	
F4	3%	2%	

\* based on the first 3 items: necroinflammatory score

### **Advanced and/or Metastatic Renal Cell Carcinoma (RCC)**

#### *Combination therapy*

Evidence supporting the use of ROFERON-A in advanced and/or metastatic RCC is derived from clinical trials investigating the combination of ROFERON-A with vinblastine or bevacizumab.

#### Study M23935

A total of 160 patients with advanced RCC were enrolled and randomised to treatment with vinblastine (*n* = 81) or with ROFERON-A and vinblastine (*n* = 79). ROFERON-A was injected SC at 3 MIU three times a week during the first week and at 18 MIU three times a week for subsequent weeks.

Vinblastine was given IV at 0.1 mg/kg once every 3 weeks to patients in both treatment groups. Treatment was continued for 1 year unless disease progression or intolerable side effects occurred. Where patients achieved a complete response, treatment was discontinued 3 months after detection of a complete response.

Median survival was 67.9 weeks in the ROFERON-A + vinblastine group and 37.4 weeks in the vinblastine group ( $p < 0.01$ ; log-rank test). In addition, median time to progression was 13 weeks in the ROFERON-A + vinblastine group and 9 weeks in the vinblastine group ( $p < 0.01$ ; log-rank test). Objective response rates (complete response + partial response) were 16.9% for ROFERON-A + vinblastine and 2.5% for vinblastine ( $p < 0.01$ ; Fisher's exact test).

During follow-up of this study, survival rates for patients treated with ROFERON-A + vinblastine or vinblastine alone were respectively, 55.7% and 38.3% after 1 year, 11.7% and 5.1% at 3 years, 8.1% and 1.3% at 4 years, and 4.1% and 0% at 5 years.

#### Study O.10519

A total of 178 patients with advanced RCC were randomised to ROFERON-A ( $n = 87$ ) or to ROFERON-A and vinblastine therapy ( $n = 91$ ). ROFERON-A was given at a dose of 18 MIU IM three times a week. Vinblastine was injected IV at a dose of 0.1 mg/kg once every 3 weeks. The dose of both drugs was reduced if WHO grade 3 or 4 toxicity developed. Treatment duration was for 6 months. However, patients with progressive disease during treatment were withdrawn. Patients with a complete response continued treatment for 6 months after the first detection of complete response. Patients with a partial response or no change after the first 6 months of treatment continued therapy for a total of 12 months. Tumours were assessed at monthly intervals.

On an intention-to-treat analysis, overall response rates were 8% in the ROFERON-A group and 19% in the ROFERON-A + vinblastine group. The difference between treatments was statistically significant ( $p = 0.038$ ). However, the difference may have resulted from a difference in performance status that existed between the two groups at baseline. Therefore it is not possible to conclude that vinblastine provides additional efficacy to that obtained with ROFERON-A alone. The median overall survival was 338 days in the ROFERON-A group and 386 days in the ROFERON-A + vinblastine group ( $p = 0.29$ ; log-rank test).

Treatment with ROFERON-A was tolerated by most patients in these studies, with reductions in dosage necessary for some. For those unable to tolerate the recommended dose of 18 MIU three times a week, halving the dose to 9 MIU did not appear to reduce the survival benefit in study M23935.

#### Study BO17705

BO17705 was a multicentre, randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of ROFERON-A in combination with bevacizumab (AVASTIN<sup>®</sup>) versus ROFERON-A alone as first-line treatment in metastatic RCC. ROFERON-A (9 MIU three times a week) plus AVASTIN (10 mg/kg every two weeks) or placebo was given until disease progression. A lower starting ROFERON-A dose (3 or 6 MIU) was permitted as long as the recommended 9

MIU dose was reached within the first 2 weeks of treatment. If 9 MIU was not tolerated, ROFERON-A dosage reduction to a minimum of 3 MIU three times a week was also permitted. In this study a benefit to patients with advanced and/or metastatic RCC was shown. A clinically relevant and statistically significant increase in progression-free survival, a trend towards an increase in overall survival and a statistically significant increase in the percentage of responders in the AVASTIN + ROFERON-A arm compared with the placebo + ROFERON-A arm were observed. However, the observed increase of 2 months in overall survival was not significant. The efficacy results are presented in Table 4.

**Table 4: Efficacy Results for Study BO17705**

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

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

For more information on the combination use with AVASTIN, refer to the AVASTIN Product Information.

### **Low Grade Non-Hodgkin's Lymphoma**

The activity of interferon alfa-2a in low-grade non-Hodgkin's lymphoma has been studied in 2 clinical trials when used as an adjunct to or concomitant with chemotherapy, with or without radiotherapy.

#### Interferon alfa-2a used as an adjunct to chemotherapy and radiotherapy

In a prospective randomised trial (Western Europe, EORTC 20856), 347 previously untreated patients with stages III or IV (working formulation categories B and C) low-grade malignant non-Hodgkin's lymphoma were treated with 8 cycles of CVP chemotherapy, followed by iceberg radiotherapy, if indicated. After induction chemo/radiotherapy, 253 patients in remission (without progressive disease) were randomised to maintenance therapy with ROFERON-A (126 patients) at 3 MIU SC or IM three times a week for 12 months, or to no further treatment. Patients were periodically assessed to determine the duration of remission and overall survival.

The median time to relapse was 135 weeks for patients treated with ROFERON-A group versus 87 weeks for those who received no-maintenance treatment; this difference was statistically significant ( $p = 0.036$ ; log-rank test). The median survival has not been reached, and the effects of treatment on overall survival have not yet been determined.

#### Interferon alfa-2a used concomitantly with chemotherapy

In a prospective randomised trial (United States, ECOG 6484), 291 patients with low or intermediate-grade NHL (working formulation categories A to E) were enrolled and eligible patients were randomised to treatment with 8 – 10 cycles of COPA chemotherapy alone, or combined with ROFERON-A at 6 MIU/m<sup>2</sup> IM on days 22 – 26 of each 28-day COPA cycle. Patients were periodically assessed for tumour responses, duration of response, time to treatment failure and survival. Patients with a partial response after 8 cycles or complete response during cycle 7 or 8 received a maximum of 2 additional treatment cycles.

After a median follow-up of 5.25 years, 81% of patients with COPA alone and 66% of patients treated with COPA plus ROFERON-A had disease progression. This difference was statistically significant ( $p = 0.0013$ ; Fisher's exact test). The study demonstrated no difference in response rate or in overall survival with addition of ROFERON-A to induction chemotherapy with COPA.

#### **Chronic Active Hepatitis B (CAHB)**

Roferon-A has been shown to induce a decrease in biochemical markers and markers of viral replication and to result in an antiviral immune response in 20 – 30% of cases of chronic active hepatitis B in the dose range equivalent to 2.5 – 10 MIU/m<sup>2</sup> (4.5 – 18 MIU).

Histological changes do not show a response greater than that seen in untreated patients.

Response to therapy is 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 HBe) markers of viral replication. Patients most likely to respond are those with mild to moderate levels of hepatitis B viral DNA.

Loss or reduction of HBs anti-genaemia usually occurs over a period of many months. The appearance of anti-HBe and in some cases anti-HBs antibody in the serum signals antiviral immunity. By 12 months after treatment there is no difference in histological, biochemical or viral markers of the disease.

#### **Chronic Myelogenous Leukaemia (CML)**

Roferon-A produces haematological remission in 60% of patients with chronic phase CML, independent of prior treatment. Two thirds of these patients have complete haematological responses which occur as late as 18 months after treatment start.

#### **Cutaneous T-Cell Lymphoma (CTCL)**

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



Partial responses are usually seen within 3 months and complete responses within 6 months, although it may occasionally take more than 1 year to reach the best response.

### **Hairy Cell Leukaemia**

During the first 1 – 2 months of treatment of patients with hairy cell leukaemia, significant depression of haematopoiesis was likely to occur. Subsequently, there was an 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 normalisation of all peripheral blood elements including haemoglobin 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%) showed a statistically significant increase compared to a historical control group (75%).

### **AIDS-Related Kaposi's Sarcoma**

Patients with AIDS-related Kaposi's sarcoma are more likely to respond to therapy if they have no history of opportunistic infection and no B symptoms (> 10% loss of body weight, fever > 38°C with no identified source of infection or night sweats). Of 182 such patients who were evaluable for efficacy, 22.5% achieved a complete or partial response.

At the recommended dose of 36 MIU, the response rate was 28.6%. Patients generally evidenced response after approximately 2 – 3 months of therapy. The response rate in patients with a prior history of opportunistic infections was less than 10%.

Responding patients experienced tumour regression. Twelve percent of responders experienced opportunistic infections during therapy whereas 20% of the poor prognosis group (B symptoms and prior opportunistic infections) had opportunistic infections during therapy on interferon. The median survival for responding patients was 51.5 months. The median survival time for non-responders was 14 months.

## **INDICATIONS**

Roferon-A is indicated for use in the treatment of:

- AIDS-related Kaposi's sarcoma
- patients with histologically proven chronic active hepatitis B (but without evidence of cirrhosis of the liver) and raised ALT levels (> 3 x upper limit of reference range)
- chronic hepatitis C given in combination with ribavirin in previously untreated patients or patients who have relapsed following alfa interferon monotherapy. Patients must be 18 years of age and have compensated liver disease.

- patients 18 years or older with histologically proven chronic hepatitis due to hepatitis C and persistently elevated serum ALT for at least 6 months and without liver decompensation (Child's Class A)
- hairy cell leukaemia
- chronic myelogenous leukaemia (CML) and excessive thrombocytosis associated with CML and other myeloproliferative disorders, in people 18 years of age or older
- cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome)
- patients with low-grade non-Hodgkin's lymphoma (as per international working formulation) when used as an adjunct to or concomitant with chemotherapy (with or without radiotherapy)
- advanced and/or metastatic renal cell carcinoma

## CONTRAINDICATIONS

Roferon-A is contraindicated in patients with:

- known hypersensitivity to alfa interferon or any component of the product.
- chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis of the liver,
- patients with autoimmune hepatitis or patients with chronic hepatitis who are being or have recently been treated with immunosuppressive agents, excluding short term "steroid withdrawal". In rare cases, severe hepatic dysfunction and liver failure with associated deaths have been reported after treatment with alfa interferon.
- neonates and infants up to the age of 3 years, because of the excipient benzyl alcohol.

Roferon-A given in combination with ribavirin must not be used in pregnant women or by men whose female partners are pregnant.

## PRECAUTIONS

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient medical record. Substitution of Roferon-A by any other biological similar product requires the consent of the prescribing physician.

### General

Roferon-A should be administered under the guidance of a qualified medical practitioner (see DOSAGE AND ADMINISTRATION). Appropriate management of the therapy and its complications is possible only when adequate diagnostic and treatment facilities are readily available.

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 judgement 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. Roferon-A may be immunogenic. Immunisation of the patient may have safety implications. As with other proteins, there is the possibility of a hypersensitivity reaction including anaphylaxis to Roferon-A administration.

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 associated with 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 Consumer Medicine Information. Patients should be well hydrated, especially during the initial stages of treatment.

Roferon-A should be used with caution in patients with severe pre-existing cardiac disease, severe renal, hepatic or myeloid dysfunction, thyroid disease, seizure disorders, neuropsychiatric disorders, and/or compromised central nervous system function.

### **Chronic Myelogenous Leukaemia**

Patients with chronic myelogenous leukaemia who have an HLA-identical relative and for whom allogeneic bone marrow transplantation is planned or possible in the immediate future should not take Roferon-A.

### **Cardiovascular**

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. However, it is likely that acute, self-limited toxicities (i.e. fever, chills) frequently associated with Roferon-A administration may exacerbate pre-existing cardiac conditions. Rarely, myocardial infarction has occurred in patients receiving Roferon-A. It is recommended that these patients are monitored.

### **Hepatic Impairment**

Caution is recommended when administering Roferon-A to chronic hepatitis patients with a history of autoimmune disease. Consequently, any patients 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 severe hepatic dysfunction and liver failure.

### **Bone Marrow Suppression**

Extreme caution should be exercised when administering Roferon-A to patients with severe myelosuppression as it has a suppressive effect on the bone marrow, leading to a fall in the white blood count, particularly granulocytes, platelet count and, less commonly, haemoglobin concentration. This can lead to increased risk of infection or haemorrhage. It is important to monitor closely these events in patients and perform a full blood count before, and at regular appropriate intervals during Roferon-A treatment.

### **Infections**

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out particularly in patients with neutropenia. Serious infections (bacterial, viral, fungal) have been reported during treatment with alfa interferons including Roferon-A. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

### **Neuropsychiatric**

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including Roferon-A. Depression, suicidal ideation, and suicide may occur in patients with and without previous psychiatric illness. Roferon-A should be used with caution in patients who report a history of depression and physicians should monitor all patients treated with Roferon-A for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of therapy, and patients should report any sign or symptoms of depression immediately. Psychiatric intervention and/or drug discontinuation should be considered in such cases.

### **Ophthalmologic**

As with other interferons, retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, retinal artery or vein thrombosis and optic neuropathy which may result in loss of vision have been reported after treatment with Roferon-A. Any patient complaining of decreased or loss of vision must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual examination prior to initiation of Roferon-A is recommended in patients with diabetes mellitus or hypertension. Roferon-A should be discontinued in patients who develop new or worsening ophthalmologic disorders.

### **Hypersensitivity**

Serious, acute hypersensitivity reactions, e.g. urticaria, angioedema, bronchoconstriction and anaphylaxis, have been rarely observed during Roferon-A therapy. If such a reaction develops during treatment of Roferon-A, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

### **Endocrine**

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

### **Autoimmune**

The development of different auto-antibodies has been reported during treatment with alfa interferons. Clinical manifestations of autoimmune disease during interferon therapy occur more frequently in subjects predisposed to the development of autoimmune disorders. Autoimmune phenomena such as vasculitis, arthritis, haemolytic anaemia, thyroid dysfunction and lupus erythematosus syndrome have been observed rarely in patients receiving Roferon-A.

Use of alfa interferon has rarely been associated with exacerbation or provocation of psoriasis.

In transplant patients (e.g. kidney or bone marrow transplant) therapeutic immunosuppression may be weakened because interferons also exert an immunostimulatory action. As with other alfa interferons, graft rejections have been reported in patients taking Roferon-A.

### **Effects on Fertility**

Roferon-A has been studied for its effect on fertility in *Macaca mulatta* (rhesus monkeys). Non-pregnant rhesus females treated with Roferon-A at doses of 5 and 25 MIU/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.

### **Use in Pregnancy – Category B3**

As with the use of other anti-cancer drugs, men and women receiving Roferon-A should practise effective contraception. In pregnancy, Roferon-A should be administered only if the benefit to the woman justifies the potential risk to the foetus. Although animal tests do not indicate that Roferon-A is a teratogen, harm to the foetus from use during pregnancy cannot be excluded. When doses greatly in excess of the recommended clinical dose were administered to pregnant rhesus monkeys in the early to mid-foetal period, an abortifacient effect was observed.

Male fertility and teratologic evaluations have yielded no significant adverse effects to date.

Roferon-A given in combination with ribavirin must not be used in pregnant women or by men whose female partners are pregnant. Fertile women and partners of fertile women should not receive ribavirin combination therapy unless the patient and his/her partner are taking efficacious contraceptive measures. Ribavirin has demonstrated significant teratogenic and/or embryocidal potential in all animal species in which adequate studies have been conducted. Based on the multiple dose half-life of ribavirin of 12 days, effective contraception must be used for 6 months post-treatment (see CONTRAINDICATIONS).

### **Use in Lactation**

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.

### **Paediatric Use**

Safety and effectiveness in children under 18 years of age have not been established.

This product contains benzyl alcohol and should not be used in neonates and infants up to the age of 3 years. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known (see CONTRAINDICATIONS).

### **Carcinogenesis and Mutagenesis**

Roferon-A has not been tested for its carcinogenic potential.

A. Internal studies: Ames tests using 6 different tester strains, with and without metabolic activation, were performed with Roferon-A up to a concentration of 1920 microgram/plate. There was no evidence of mutagenicity.

Human lymphocyte cultures were treated *in vitro* with Roferon-A at non-cytotoxic 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 leucocyte interferon have been reported.

A chromosomal defect following the addition of human leucocyte 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 leucocyte interferon.

It has also been shown that human leucocyte interferon protects primary chick embryo fibroblasts from chromosomal aberrations produced by gamma rays.

### **Effects on 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 response of hairy cell leukaemia or AIDS-related Kaposi's sarcoma is not generally observed for 1 – 3 months after initiation of treatment, very careful monitoring for severe depression of blood cell counts is warranted during the initial phase of treatment.

For patients with hairy cell leukaemia, tests should be performed to quantitate peripheral hairy cells and bone marrow hairy cells prior to initiation of therapy.

For patients with AIDS-related Kaposi's sarcoma, indicator lesion measurements and total lesion count should be performed before initiation of therapy. These parameters should be monitored periodically (e.g. monthly) during treatment to determine whether response to treatment or disease stabilisation has occurred.

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

Thyroid abnormalities were detected in patients treated for chronic hepatitis C with Roferon-A therapy in approximately 1% of patients with no thyroid function abnormalities at baseline. A third of these patients with pre-existing abnormalities worsened during therapy. In patients treated for chronic hepatitis C, thyroid functions should be assessed prior to the initiation of Roferon-A and re-evaluated during the course of therapy if symptoms consistent with thyroid dysfunction develop.

A liver biopsy should be performed in all patients considered for treatment of hepatitis. Patients with causes of hepatitis other than chronic hepatitis B or chronic hepatitis C should be excluded. Patients treated with Roferon-A for chronic hepatitis B or C should be appropriately monitored because of the increased risks of hepatic decompensation in association with a flare of aminotransaminases.

### **Effects on Ability to Drive and Operate Machinery**

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.

## INTERACTIONS WITH OTHER MEDICINES

Interactions between Roferon-A and other drugs have not been fully evaluated.

Since alfa interferons alter cellular metabolism, the potential exists for Roferon-A to modify the activity of other drugs. In a small study, Roferon-A was shown to have an effect on specific microsomal enzyme systems. The clinical relevance of these findings is unknown (see PHARMACOLOGY).

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 metabolised by this route. Reduced clearance of theophylline following the concomitant administration of alfa interferons has been reported.

It has been observed that the neurotoxic, haematotoxic or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons. Interactions could occur following concurrent administration of centrally-acting drugs.

Pulmonary symptoms have been reported more frequently when sho-saiko-to, a Chinese herbal medicine, also known as Xiao-Chai-Hu was given with interferon alfa-2a. This herb should not be taken by patients receiving interferon.

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

## ADVERSE EFFECTS

### Roferon-A Monotherapy

The following data on adverse reactions are based on information derived from the treatment of cancer patients with a wide variety of malignancies and often refractory to previous therapy and suffering from advanced disease, patients with chronic hepatitis B and patients with chronic hepatitis C. Most cancer patients received doses that were significantly higher than the dose now recommended and this probably explains the higher frequency and severity of adverse reactions in this patient group compared with patients with hepatitis B where adverse reactions are usually transient, and patients return to pre-treatment status within 1 – 2 weeks after the end of therapy.

*Haematopoietic system. Common:* Transient leucopenia rarely requires restriction of dosage, in myelosuppressed patients, thrombocytopenia and decreased haemoglobin. *Uncommon:* In non-myelosuppressed patients, thrombocytopenia. *Rare:* Decrease of haemoglobin and haematocrit. Recovery of severe haematological deviations to pretreatment levels usually occurred within 7 – 10 days after discontinuing Roferon-A treatment. *Very rare:* Idiopathic thrombocytopenic purpura (ITP).

*Vision disorders. Uncommon:* Visual disturbances. *Rare:* Ischaemic retinopathy. *Very rare:* Retinopathy including retinal haemorrhages and cotton wool spots, papilloedema, retinal artery and vein thrombosis and optic neuropathy.

*Gastrointestinal tract. Frequent:* About two thirds of cancer patients experienced anorexia and one half nausea. *Common:* Emesis, taste alterations, mouth dryness, weight loss, diarrhoea and mild or

moderate abdominal pain. *Rare:* Constipation, flatulence, hypermotility, heartburn, reactivation of peptic ulcer, non-life-threatening gastrointestinal bleeding as well as reversible pancreatic reactions i.e. amylase/lipase increase with or without abdominal pain.

*General symptoms. Frequent:* Patients experienced flu-like symptoms, e.g. fatigue, fever, chills, appetite loss, myalgia, headache, arthralgia and diaphoresis. These acute side effects can usually be reduced or eliminated by concurrent administration of paracetamol and tend to diminish with continued therapy or dose moderation. Continuing therapy can lead to lethargy, weakness and fatigue.

*Alterations of hepatic function. Uncommon:* Elevation of ALT but also of alkaline phosphatase, lactate dehydrogenase and bilirubin, which generally did not require dosage adjustment. In rare cases jaundice, hepatitis, hepatic failure and hepatic encephalopathy were reported. *Rare:* In hepatitis B, changes in transaminases usually signal clinical improvement.

*Abnormal Laboratory Test Values. Common:* Mild and less commonly moderate declines in neutrophils and leucocytes, declines in haemoglobin, haematocrit and platelets. *Rare:* Severe declines in haemoglobin, haematocrit and platelets, abnormalities in serum SGOT of mild to moderate degree, increases in alkaline phosphatase and LDH, proteinuria, hypocalcaemia, hyperbilirubinaemia, hyperglycaemia and abnormalities of serum uric acid, BUN and creatinine. These effects tend to be dose-dependent and improve spontaneously or with dose attenuation or discontinuation of therapy.

*Central nervous system. Uncommon:* Dizziness, vertigo, decreased mental status, forgetfulness, depression, drowsiness, confusion, behavioural disturbances, such as anxiety and nervousness, sleep disturbances. *Rare:* Suicidal ideation, suicide attempt, suicide, severe somnolence, convulsions, coma, cerebrovascular adverse events and transient impotence.

*Peripheral nervous system. Uncommon:* Paraesthesia, numbness, neuropathy, itching and tremor.

*Renal and urinary system. Rare:* Decreased renal function, acute renal failure mainly in cancer patients with renal diseases and/or nephrotoxic comedications as concomitant risk factors, electrolyte disturbances generally in association with anorexia or dehydration, proteinuria and increased cell count in sediment, elevation of BUN, serum creatinine and uric acid.

*Cardiovascular and pulmonary systems. Common:* Disorders were seen in about one fifth of cancer patients and consisted of transient hypotensive and hypertensive episodes, oedema, cyanosis, arrhythmias, palpitations and chest pain. *Rare:* Coughing, mild dyspnoea, pneumonia, pulmonary oedema, congestive heart failure, cardiorespiratory arrest and myocardial infarction. *Very rare:* Cardiovascular problems in patients with hepatitis B.

*Skin, mucous membranes and adnexa. Common:* Mild to moderate alopecia occurred in up to one fifth of patients, but this was reversible on discontinuation of treatment. Note that alopecia may continue for several weeks after discontinuation of treatment. *Rare:* Re-exacerbation of herpes labialis, rash, pruritus, dryness of skin and mucous membranes, rhinorrhoea and epistaxis.



If Roferon-A is used concomitantly with combination chemotherapy, haematological toxicity may be exacerbated, requiring reduction of doses of other myelosuppressive drugs in the chemotherapy regimen.

*Other. Rare:* Hyperglycaemia, diabetes mellitus, injection site reactions at injection sites, including very rarely, necrotic site reactions, autoimmune phenomena i.e. vasculitis, arthritis, haemolytic anaemia, thyroid dysfunction and lupus erythematosus syndrome. *Very rare:* asymptomatic hypocalcaemia, sarcoidosis, elevated serum glucose, hypertriglyceridaemia/hyperlipidaemia.

### Roferon-A Combination Therapy

The following adverse reactions are based on clinical experience of Roferon-A in combination with ribavirin in chronic hepatitis C patients.

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

**Table 5. Treatment related adverse reactions  $\geq 4\%$  of patients with chronic hepatitis C**

	Relapsed patients		Previously untreated patients		
	Roferon-A + Ribavirin <i>n</i> = 49 (%)	Roferon-A <i>n</i> = 50 (%)	Roferon-A + Ribavirin <i>n</i> = 21 (%)	Roferon-A <i>n</i> = 19 (%)	Placebo <i>n</i> = 20 (%)
Body as a Whole					
Asthenia	73	68	71	53	50
Influenza-like symptoms	35	34	-	-	-
Fever	8	6	-	-	-
Psychiatric					
Insomnia	27	14	43	47	15
Irritability	24	10	29	42	35
Depression	14	14	29	42	35
Anorexia	8	4	+	+	+
Neurological					
Headache	22	18	-	-	-
Dizziness	8	8	-	-	-
Paraesthesia	4	2	-	-	-
Tremor	4	0	-	-	-
Respiratory					
Dyspnoea	18	6	-	-	-
Coughing	6	0	-	-	-
Skin and Subcutaneous Tissues					-
Alopecia	18	20	62●	58●	20●
Pruritus	16	4	-	-	-
Skin dry	8	2	-	-	-
Rash erythematous	4	4	0	11	0
Eczema	4	0	-	-	-
Gastrointestinal					
Nausea	16	6	24+	26+	10+
Dyspepsia	10	0	-	-	-
Vomiting	8	2	-	-	-
Dry mouth	6	2	-	-	-

	Relapsed patients		Previously untreated patients		
	Roferon-A +	Roferon-A	Roferon-A +	Roferon-A	Placebo
Abdominal pain	4	6	-	-	-
Diarrhoea	4	4	14	16	5
Metabolic and Nutritional					
Weight decrease	8	6	24	47	10
Musculoskeletal					
Arthralgia	6	8	38	53	10
Myalgia	6	12	-	-	-
Blood					
Epistaxis	6	2	-	-	-
Special senses					
Taste perversion	4	0	-	-	-
Cardiovascular					
Palpitations	0	4	-	-	-

+ listed as anorexia and nausea, • listed as mild hair loss.

### Laboratory Test Values

In clinical trials conducted with Roferon-A with ribavirin, the majority of cases of abnormal laboratory values were managed with dose modifications.

Thyroid function test abnormalities requiring clinical intervention occur in less than 5% of patients with no previous thyroid disorder.

An increase in uric acid and indirect bilirubin values associated with haemolysis were observed in some patients treated Roferon-A in combination with ribavirin and values returned to baseline levels within 4 weeks after end of therapy. In no case was this associated with clinical manifestations and values returned to baseline levels within 4 weeks after the end of treatment.

Anaemia was the primary reason for ribavirin dose reductions during clinical trials, which occurred in 19% of patients treated with ribavirin in combination with interferon alfa-2a.

### Post-Marketing Experience

The following adverse reactions have been identified during post-marketing use of Roferon-A. As these events are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency.

*Immune System Disorders:* as with other alfa interferons, graft rejections have been reported in patients taking Roferon-A.

*Psychiatric Disorders:* mania has been reported.

*Gastrointestinal Disorders:* haemorrhagic/ischemic colitis and ulcerative colitis have been reported.

## DOSAGE AND ADMINISTRATION

### Chronic Hepatitis C

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

### Roferon-A Monotherapy

The recommended dose of Roferon-A is 3 MIU administered three times a week by subcutaneous (SC) injection for 12 months. Patients whose serum ALT has not normalised during the initial 3 months of treatment are unlikely to respond and treatment should be discontinued.

### Roferon-A in Combination with Ribavirin (Copegus®) Therapy

The recommended dose of Roferon-A is 4.5 MIU three times a week SC for a period of 24 weeks. The recommended dose of ribavirin is dependent on the patients' body weight (see Table 6).

**Table 6: Ribavirin dosing recommendations in combination with Roferon-A**

Patient weight	Daily ribavirin dose	Number of 200 mg tablets to be taken	
		morning	evening
< 75 kg	1000 mg	2	3
≥ 75 kg	1200 mg	3	3

If severe adverse reactions or laboratory abnormalities develop during Roferon-A with ribavirin combination therapy modify the doses of each product until the adverse reactions abate. If intolerance persists after dose adjustment, discontinuation of ribavirin or both Roferon-A and ribavirin may be necessary.

**Table 7. Dosage Modification Guidelines**

Laboratory Values	Reduce only ribavirin dose to 600 mg /day if*:	Discontinue ribavirin if**:
Haemoglobin: patients with no cardiac disease	<100 g/L	<85 g/L
Haemoglobin: patients with history of stable cardiac disease	≥20 g/L decrease in haemoglobin during any 4 week period during treatment (permanent dose reduction)	<120 g/L after 4 weeks of dose reductions

\* Patients whose dose of ribavirin is reduced to 600 mg daily receive only one 200 mg tablet in the morning and two 200 mg tablets in the evening.

\*\* If the abnormality is reversed, ribavirin may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to original dosing is not recommended.

### **Advanced and/or Metastatic Renal Cell Carcinoma (RCC)**

#### Roferon-A Monotherapy

Roferon-A should be given SC at a dose of 3 MIU three times a week for one week, 9 MIU three times a week for the following week and 18 MIU three times a week thereafter.

If the Roferon-A dose of 18 MIU three times a week is not tolerable, the dose may be reduced to 9 MIU three times a week.

Treatment should be given for a minimum of 3 months, up to a maximum of 12 months or until the development of progressive disease. Patients who achieve a complete response may stop treatment 3 months after the response is established.

#### Roferon-A in Combination with Bevacizumab (AVASTIN)

Roferon-A should be given SC at a dose of 9 MIU three times a week until disease progression or for up to 12 months.

Roferon-A therapy may be initiated with a lower dose (3 or 6 MIU). However, the recommended dose of 9 MIU should be reached within the first 2 weeks of treatment.

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

Roferon-A injections are given after completion of the AVASTIN infusion.

For more information on the combination use with AVASTIN, refer to the AVASTIN Product Information.

### **Low-Grade Non-Hodgkin's Lymphoma**

Roferon-A should be given as maintenance after conventional chemotherapy (with or without radiotherapy) at a dose of 3 MIU SC three times a week for up to 12 months. Roferon-A should be commenced as soon as the patient recovers from the effects of chemo-radiotherapy, usually after 4 – 6 weeks.

Roferon-A may also be administered concomitantly to a conventional chemotherapy regimen (such as the combination of cyclophosphamide, prednisone, vincristine and doxorubicin) according to a schedule such as 6 MIU/m<sup>2</sup> SC from day 22 – day 26 of each 28 day cycle. When given concomitantly with chemotherapy, Roferon-A may be commenced in conjunction with chemotherapy.

### **Chronic Active Hepatitis B**

The recommended dose is 4.5 MIU SC three times a week for 6 months. If genomic markers of viral replication or HBe antigen in the serum do not decrease after 1 month of therapy the dose should be escalated to the next level. Dosages may be increased to the limit of the patient's tolerance, up to a maximum of 18 MIU three times a week for 3 – 6 months. The appearance of anti-HBe antibody associated with loss of genomic markers for viral replication is indicative of an adequate early response to therapy.

There is no evidence that response to interferon is dose related. Doses need not be increased in patients who show an adequate “flare” response (i.e. > 3 x increase in ALT levels) during the first few weeks of treatment.

### **Chronic Myelogenous Leukaemia**

It is recommended that Roferon-A be given SC for 8 – 12 weeks to patients 18 years of age or more.

The recommended schedule is:

Days 1 – 3: 3 MIU daily

Days 4 – 6: 6 MIU daily

Days 7 – 84: 9 MIU daily

*Duration of treatment:* Patients should be treated for a minimum of 8 weeks, preferably for at least 12 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 haematological parameters. Responding patients should be treated until complete haematological response is achieved or for a maximum of 18 months. All patients with complete haematological responses should then continue treatment with 9 MIU daily (optimum) or 9 MIU 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 leukaemia has not been determined, although cytogenetic responses have been observed 2 years after treatment start.

### **Thrombocytosis Associated with CML and Other Myeloproliferative Disorders**

Thrombocytosis is a frequent concomitant phenomenon in CML and is the hallmark of essential thrombocythaemia. The morbid nature of severe thrombocytosis is reflected by the frequent manifestation of a serious thrombotic or haemorrhagic diathesis.

Interferon alfa-2a has been clearly shown to:

- a. cause a decrease in excessive platelet counts within a few days
- b. reduce the frequency of thrombocytosis associated thrombo-haemorrhagic complications
- c. have no leukemogenic potential

Therefore, it is recommended that a non-leukemogenic therapy is undertaken with interferon alfa-2a for the treatment of patients with excessive thrombocytosis in CML, even in the absence of cytogenetic response, and in other myeloproliferative disorders.

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

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

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

A well tolerated dose of 1 – 3 MIU daily, 2 – 3 times a week, is usually enough to maintain platelet counts within the normal range. The dose, however, needs to be titrated individually for each patient to his/her highest tolerated dose.

### **Hairy Cell Leukaemia**

The induction dose of Roferon-A is 3 MIU SC daily for 16 – 24 weeks. The recommended maintenance dose is 3 MIU, three times a 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 MIU is not recommended. The minimum effective dose of Roferon-A for treatment of hairy cell leukaemia has not been established.

Patients should be treated for approximately 6 months before the physician determines whether to continue therapy in patients who respond or discontinue therapy in patients who do not respond. Patients with hairy cell leukaemia have been treated for up to 20 consecutive months. The optimal duration of treatment for this disease has not been determined.

### **Cutaneous T-Cell Lymphoma**

*Initial dosage:* Roferon-A should be given by subcutaneous injection, and escalated to 18 MIU daily for a total of 12 weeks in patients of 18 years or older. The recommended escalation schedule is as follows:

- Days 1 – 3: 3 MIU daily

Days 4 – 6: 9 MIU daily  
Days 7 – 10: 18 MIU daily

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

*Duration of treatment:* Patients should be treated for a minimum of 8 weeks and preferably for at least 12 weeks before the physician decides whether to continue treatment in responding patients or to discontinue treatment in non-responding patients. Minimum treatment duration in responding patients should be 12 months in order to maximise the chance to achieve a complete response and improve the chance for a prolonged response.

Patients have been treated for up to 40 consecutive months. The optimal duration of Roferon-A treatment for cutaneous T-cell lymphoma has not been determined.

### **AIDS-Related Kaposi's Sarcoma**

The induction dose of Roferon-A is 36 MIU daily for 4 weeks, extended to 10 – 12 weeks if the treatment is well-tolerated. The recommended maintenance dose is 36 MIU three times a week. Dosage reductions by one-half or withholding of individual doses may be required when severe adverse reactions occur. The use of doses higher than 36 MIU is not recommended.

Patients who evidence disease stabilisation or response should be treated until a complete response, with disappearance of all active tumour, is achieved. The optimal duration of treatment for this disease has not been determined.

### **Dosage Modification For Adverse Reactions**

If the severity of constitutional adverse reactions do not diminish on continued treatment (tachyphylaxis) at the recommended dose, or cannot be controlled by concomitant symptomatic medication or by administering Roferon-A in the evening, then the dose of Roferon-A should be reduced to a level which, in terms of adverse reactions, is considered acceptable by the patient and the physician. If severe adverse events occur, it is recommended that the dose should be reduced by 50% or that treatment should be temporarily discontinued. It is safe to recommence therapy at a reduced dosage.

Dosage should be modified to take into account the constitutional symptoms, the myelosuppressive effects or other clinical or laboratory test abnormalities caused by Roferon-A and concurrently administered drugs or the effects of previous x-irradiation therapy or chemotherapy which may have reduced bone marrow reserve.

If severe adverse reactions or laboratory abnormalities develop during Roferon-A with ribavirin combination therapy, modify the dosages of each component as appropriate, until the adverse reactions abate (see Table 7).

### **Administration**

The subcutaneous route of administration should be used for the pre-filled syringes.

The syringe requires no preparation prior to administration.

## **OVERDOSAGE**

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

Contact the Poisons Information Centre (phone: 13 11 26) for advice on management of overdose.

## **PRESENTATION AND STORAGE CONDITIONS**

- Pre-filled syringe containing 3 MIU/0.5 mL + 1 needle for SC injection
- Pre-filled syringe containing 9 MIU/0.5mL + 1 needle for SC injection

All strengths are for single dose use. The pre-filled syringes should be used once only and any residue discarded.

### **Storage**

Store the pre-filled syringes at 2°C – 8°C in a refrigerator. Do not freeze. Protect from light.

### **Disposal of Medicines**

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

## **NAME AND ADDRESS OF THE SPONSOR**

Roche Products Pty Limited  
ABN 70 000 132 865  
Level 8, 30-34 Hickson Road  
Sydney  
AUSTRALIA

Medical Enquiries: 1800 233 950

## **POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine – S4

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)**

20 May 1997

## **DATE OF MOST RECENT AMENDMENT:**

26 September 2017