Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Roferon-A 4.5 million international units (IU) solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 4.5 million International Units interferon alfa-2a* per 0.5 millilitres** (4.5 million IU/0.5ml).

*produced in Escherichia coli by recombinant DNA technology
**Contains volume overages.

For the full list of excipients, see section 6.1.
Excipients recognised to have a known effect:
Benzyl alcohol (10mg/1ml)

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Solution is clear and colourless to light yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Roferon-A is indicated for the treatment of:

- Hairy cell leukemia.

- AIDS patients with progressive, asymptomatic Kaposi's sarcoma who have a CD4 count > 250/mm^3.

- Chronic phase Philadelphia-chromosome positive chronic myelogenous leukemia. Roferon-A is not an alternative treatment for CML patients who have an HLA-identical relative and for whom allogeneic bone marrow transplantation is planned or possible in the immediate future. It is still unknown whether Roferon-A can be considered as a treatment with a curative potential in this indication.

- Cutaneous T-cell lymphoma. Interferon alfa-2a (Roferon-A) may be active in patients who have progressive disease and who are refractory to, or unsuitable for, conventional therapy.

- Adult patients with histologically proven chronic hepatitis B who have markers for viral replication, i.e., those who are positive for HBV DNA or HBeAg.

- Adult patients with histologically proven chronic hepatitis C who are positive for HCV antibodies or HCV RNA and have elevated serum alanine aminotransferase (ALT) without liver decompensation.

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

- Follicular non-Hodgkin’s lymphoma.

- Advanced renal cell carcinoma.

- Patients with AJCC stage II malignant melanoma (Breslow tumour thickness > 1.5 mm, no lymph node

involvement or cutaneous spread) who are free of disease after surgery.

4.2 Posology and method of administration

Not all available Roferon-A strengths can be used for all indications mentioned in section 4.1. The prescribed strength should correspond with the recommended dose for each individual indication.

- HAIRY CELL LEUKEMIA

Initial dosage:

Three million IU daily, given by subcutaneous injection for 16 − 24 weeks. If intolerance develops, either the daily dose should be lowered to 1.5 million IU or the schedule changed to three times per week, or both.

Maintenance dosage:

Three million IU, given three times per week by subcutaneous injection. If intolerance develops, the dose should be lowered to 1.5 million IU three times per week.

Duration of treatment:

Patients should be treated for approximately six months before the physician decides whether to continue treatment in responding patients or to discontinue treatment in non-responding patients. Patients have been treated for up to 20 consecutive months. The optimal duration of Roferon-A treatment for hairy cell leukemia has not been determined.

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

- AIDS−RELATED KAPOSI'S SARCOMA

Roferon-A is indicated for the treatment of AIDS patients with progressive, asymptomatic Kaposi’s sarcoma who have a CD4 count > 250/mm^3. AIDS patients with CD4 counts < 250/mm^3 , or those with a history of opportunistic infections or constitutional symptoms, are unlikely to respond to Roferon-A therapy and therefore should not be treated. The optimal posology has not yet been well established.

Roferon-A should not be used in conjunction with protease inhibitors. With the exception of zidovudine, there is a lack of safety data for the combination of Roferon-A with reverse transcriptase inhibitors.

Initial dosage:

Roferon-A should be given by subcutaneous injection, and escalated to at least 18 million IU daily and if possible to 36 million IU daily for a total of ten to twelve weeks in patients of 18 years or older. The recommended escalation schedule is as follows:

days 1−3	3 million IU daily
days 4−6	9 million IU daily
days 7−9	18 million IU daily − and, if tolerated, increase to:
days 10−84	36 million IU daily

Maintenance dosage:

Roferon-A should be given by subcutaneous injection three times per week at the maximum dose which is acceptable to the patient, but not exceeding 36 million IU.

Patients with AIDS−related Kaposi's sarcoma treated with 3 million IU of Roferon-A given daily showed a lower response rate than those treated with the recommended dosage.

Duration of treatment:

The evolution of lesions should be documented to determine response to therapy. Patients should be treated for a minimum of 10 weeks and preferably for at least twelve weeks before the physician decides whether to continue treatment in responding patients or to discontinue treatment in non−responding patients. Patients generally showed evidence of response after approximately three months of therapy. Patients have been treated for up to 20 consecutive months. If a response to treatment occurs, treatment should continue at least until there is no further evidence of tumour. The optimal duration of Roferon-A treatment for AIDS−related Kaposi's sarcoma has not been determined.

Note:

Lesions of Kaposi's sarcoma frequently reappear when Roferon-A treatment is discontinued.

- CHRONIC MYELOGENOUS LEUKEMIA

Roferon-A is indicated for the treatment of patients with chronic phase Philadelphia-chromosome positive chronic myelogenous leukemia. Roferon-A is not an alternative treatment for CML patients who have an HLA-identical relative and for whom allogeneic bone marrow transplantation is planned or possible in the immediate future.

Roferon-A produces haematological remissions 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.

In contrast to cytotoxic chemotherapy, interferon alfa-2a is able to generate sustained, ongoing cytogenetic responses beyond 40 months. It is still unknown whether Roferon-A can be considered as a treatment with a curative potential in this indication.

Dosage:

It is recommended that Roferon-A should be given by subcutaneous injection for eight to 12 weeks to patients 18 years or more. The recommended schedule is:

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

Duration of treatment:

Patients should be treated for a minimum of eight weeks, preferably for at least twelve weeks before the physician decides whether or not to continue treatment in responding patients or to discontinue treatment in patients not showing any changes in haematological parameters. Responding patients should be treated until complete haematological response is achieved or for a maximum of 18 months. All patients with complete hematologic responses should continue treatment with 9 million IU daily (optimum) or 9 million IU three times a week (minimum) in order to achieve a cytogenetic response in the shortest possible time. The optimal duration of Roferon-A treatment for chronic myelogenous leukemia has not been determined, although cytogenetic responses have been observed two years after treatment start.

The safety, efficacy and optimal dosage of Roferon-A in children with CML has not yet been established.

- CUTANEOUS T-CELL LYMPHOMA (CTCL)

Interferon alfa-2a (Roferon-A) may be active in patients with progressive cutaneous T-cell lymphoma and who are refractory to, or unsuitable for conventional therapy.

The optimal dosage has not been established.

Initial dosage:

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

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

Maintenance dosage:

Roferon-A should be given by subcutaneous injection three times per week at the maximum dose which is acceptable to the patient, but not exceeding 18 million IU.

Duration of treatment:

Patients should be treated for a minimum of eight weeks and preferably for at least twelve weeks before the physician decides whether to continue treatment in responding patients or to discontinue treatment in 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.

Warning:

Objective tumour responses have not been observed in approximately 40% of patients with CTCL. Partial responses are usually seen within 3 months and complete responses within 6 months, although it may occasionally take more than one year to reach the best response.

- CHRONIC HEPATITIS B

Roferon-A is indicated for the treatment of adult patients with histologically proven chronic hepatitis B who have markers for viral replication, i.e., those who are positive for HBV DNA or HBeAg.

Dosage recommendation:

The optimal schedule of treatment has not been established yet. The dose is usually in the range of 2.5 million IU to 5.0 million IU/m^2 body surface administered subcutaneously three times per week for a period of 4 to 6 months.

The dosage may be adjusted according to the patient's tolerance to the medication. If no improvement has been observed after 3−4 months of treatment, discontinuation of therapy should be considered.

Children: up to 10 million IU/m2 has been safely administered to children with chronic hepatitis B. However efficacy of therapy has not been demonstrated.

- CHRONIC HEPATITIS C

ROFERON-A IN COMBINATION WITH RIBAVIRIN

RELAPSED PATIENTS

Roferon-A is given in combination with ribavirin for adult patients with chronic hepatitis C who have previously responded to interferon alpha monotherapy, but who have relapsed after treatment was stopped.

Dosage:

Roferon-A: 4.5 million IU 3 times per week by subcutaneous injection for a period of 6 months.

Dosage of Ribavirin:

Ribavirin dose: 1000 mg to 1200 mg/day in two divided doses (once in the morning with breakfast and once with the evening meal). Please refer to the SmPC for ribavirin for further details on the posology and method of administration of ribavirin.

NAÏVE PATIENTS

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

Dosage:

Roferon-A: 3 to 4.5 million IU 3 times per week by subcutaneous injection for a period of at least 6 months. Treatment should be continued for an additional 6 months in patients who have negative HCV RNA at month 6, and are infected with genotype 1 and have high pretreatment viral load.

Dosage of Ribavirin: see above

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

Patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) do generally not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

ROFERON-A MONOTHERAPY

Roferon-A monotherapy should be given mainly in case of intolerance or contraindication to ribavirin.

Initial dosage:

Roferon-A should be administered at a dose of 3 to 6 million IU by subcutaneous injection three times a week for six months as induction therapy, patient tolerance permitting. In patients who fail to respond after three to four months of treatment, discontinuation of Roferon-A should be considered.

Maintenance dosage:

Patients whose serum ALT has normalized and/or HCV RNA has become undetectable require maintenance therapy with 3 million IU Roferon-A three times a week for an additional six months or longer to consolidate the complete response. The optimal duration of treatment has not yet been determined but a therapy of at least 12 months is advised.

Note:

The majority of patients who relapse after adequate treatment with Roferon-A alone do so within four months of the end of treatment.

- FOLLICULAR NON-HODGKINS LYMPHOMA

Roferon-A prolongs disease-free and progression-free survival when used as adjunctive treatment to CHOP-like chemotherapy regimens in patients with advanced (high tumour burden) follicular non-Hodgkin’s lymphoma. However, the efficacy of adjunctive interferon alfa-2a treatment on overall long-term survival of these patients has not

yet been established.

Dosage Recommendation:

Roferon-A should 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 million IU/m^2 given subcutaneously from day 22 to day 26 of each 28-day cycle.

- ADVANCED RENAL CELL CARCINOMA

COMBINATION WITH VINBLASTINE

Therapy with Roferon-A in combination with vinblastine induces overall response rates of approximately 17-26%, delays disease progression, and prolongs overall survival in patients with advanced renal cell carcinoma.

Dosage recommendation:

Roferon-A should be given by subcutaneous injection at a dose of 3 million IU three times weekly for one week, 9 million IU three times weekly for the following week and 18 million IU three times weekly thereafter. Concomitantly, vinblastine should be given intravenously according to the manufacturer's instructions at a dose of 0.1 mg/kg once every 3 weeks.

If the Roferon-A dosage of 18 million IU three times per week is not tolerated the dose may be reduced to 9 million IU three times per week.

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

COMBINATION WITH BEVACIZUMAB (AVASTIN)

Dosage recommendation:

9 million IU by subcutaneous injection three times weekly until disease progression or up to 12 months. The safety and efficacy of Roferon-A therapy after 12 months have not been evaluated.
Roferon-A therapy may be initiated with a lower dose (3 or 6 million IU), the recommended dose of 9 million IU should however be reached within the first 2 weeks of treatment.
If the Roferon-A dosage of 9 million IU three times per week is not tolerated, the dosage may be reduced to a minimum dosage of 3 million IU three times per week.

Roferon-A injections are given after completion of the Avastin infusion. For more information on combination use with Avastin, refer to the Avastin SmPC.

- SURGICALLY RESECTED MALIGNANT MELANOMA.

Adjuvant therapy with a low dose of Roferon-A prolongs disease-free interval in patients with no nodal or distant metastases following resection of a melanoma (tumour thickness > 1.5 mm).

Dosage recommendation:

Roferon-A should be administered subcutaneously at a dose of 3 million IU three times a week for 18 months, starting no later than six weeks post-surgery. If intolerance develops, the dose should be lowered to 1.5 million IU three times a week.

4.3 Contraindications

Roferon-A is contraindicated in patients with:

- A history of hypersensitivity to recombinant interferon alfa-2a or to any of the excipients listed in section 6.1,
- Patients with severe pre-existing cardiac disease or with any history of cardiac illness. No direct cardiotoxic effect has been demonstrated, but it is likely that acute, self−limiting toxicities (i.e., fever, chills) frequently associated with administration of Roferon-A may exacerbate pre-existing cardiac conditions,
- Severe renal, hepatic or myeloid dysfunction,
- Uncontrolled seizure disorders and/or compromised central nervous system function (see section 4.4.),
- Chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis of the liver,
- Chronic hepatitis who are being or have recently been treated with immunosuppressive agents,
- Benzyl alcohol, which is an excipient in Roferon-A solution for injection has on rare occasions been associated with potentially fatal toxicities and anaphylactoid reactions in children up to 3 years old. Therefore, Roferon-A solution for injection should not be used in premature babies, neonates, infants or children up to 3 years old. Roferon-A solution contains 10 mg/ml benzyl alcohol.

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

4.4 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file.

Roferon-A should be administered under the supervision of a qualified physician experienced in the management of the respective indication. Appropriate management of the therapy and its complications is possible only when adequate diagnostic and treatment facilities are readily available.

Patients should be informed not only of the benefits of therapy but also that they will probably experience adverse reactions.

Hypersensitivity: If a hypersensitivity reaction occurs during treatment with Roferon-A or in the combination therapy with ribavirin, treatment has to be discontinued and appropriate medical therapy has to be instituted immediately. Transient rashes do not necessitate interruption of treatment.

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 alpha interferons, graft rejections have been reported in patients taking Roferon-A.

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

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

Patients with substance use/abuse: HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha

interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

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 decrease or loss of vision must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual examination prior to initiation of Roferon-A monotherapy or in the combination therapy with ribavirin is recommended in patients with diabetes mellitus or hypertension. Roferon-A monotherapy or the combination therapy with ribavirin should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Endocrine: Hyperglycaemia has been observed rarely in patients treated with Roferon-A. All patients who develop symptoms of hyperglycaemia should have their blood glucose measured and followed-up accordingly. Patients with diabetes mellitus may require adjustment of their antidiabetic regimen.

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

Hepatic function: In rare cases interferon alpha has been suspected of causing an exacerbation of an underlying autoimmune disease in hepatitis patients. Therefore, when treating hepatitis patients with a history of autoimmune disease, caution is recommended. If a deterioration in liver function develops in these patients, a determination of autoimmune antibodies should be considered. If necessary, treatment should be discontinued.

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 an increased risk of infection or of haemorrhage. It is important to monitor closely these events in patients and periodic complete blood counts should be performed during the course of Roferon-A treatment, both prior to therapy and at appropriate periods during therapy.

Autoimmune: The development of different auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy occur more frequently in subjects predisposed to the development of autoimmune disorders. In patients with an underlying or clinical history of auto-immune disorders, monitoring of symptoms suggestive of these disorders, as well as measurement of auto antibodies and TSH level, is recommended.

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

Efficacy in patients with chronic hepatitis B or C who are on haemodialysis or have haemophilia or are coinfected with human immunodeficiency virus has not been demonstrated.

This product contains less than 1 mmol sodium (23 mg) per 0.5 ml, i.e. essentially ‘sodium-free’.

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

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Roferon-A and ribavirin to HAART therapy (see ribavirin SPC).

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this

patient subset.

4.5 Interaction with other medicinal products and other forms of interaction

Since alpha−interferons alter cellular metabolism, the potential to modify the activity of other drugs exists. 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.

Alpha−interferons may affect the oxidative metabolic process; this should be borne in mind when prescribing concomitant therapy with drugs metabolised by this route. However, as yet no specific information is available.

Roferon-A has been reported to reduce the clearance of theophylline.

As Roferon-A may affect central nervous system functions, interactions could occur following concurrent administration of centrally−acting drugs. The neurotoxic, haematotoxic or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons.

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

Results from a controlled clinical study in renal cancer patients demonstrated no significant effect of bevacizumab (Avastin) on the pharmacokinetics of interferon alfa-2a (Roferon-A).

4.6 Fertility, pregnancy and lactation

Men and women receiving Roferon-A should practise effective contraception. There are no adequate data on the use of Roferon-A in pregnant women. 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 (see section 5.3). Although animal tests do not indicate that Roferon-A is a teratogen, harm to the foetus from use during pregnancy cannot be excluded. In pregnancy, Roferon−A should be administered only if the benefit to the woman justifies the potential risk to the foetus.

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

Use with ribavirin in patients with chronic hepatitis C
Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin therapy is contraindicated in women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking Roferon-A in combination with ribavirin. Female patients of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded. Please refer to the ribavirin SPC.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, depending on dose and schedule as well as the sensitivity of the individual patient, Roferon-A may have an effect on the speed of reaction which could impair certain operations, e.g., driving, operation of machinery etc.

4.8 Undesirable effects

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

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.

Approximately two thirds of cancer patients experienced anorexia and one half nausea. Cardiovascular and pulmonary disorders were seen in about one fifth of cancer patients and consisted of transient hypotension, hypertension, oedema, cyanosis, arrhythmias, palpitations and chest pain. Most cancer patients received doses that were significantly higher than the dose now recommended and may explain 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 to 2 weeks after the end of therapy. Cardiovascular disorders were very rarely seen in patients with hepatitis B. In hepatitis B patients, changes in transaminases usually signal an improvement in the clinical state of the patient.

The majority of the patients experienced flu−like symptoms such as fatigue, pyrexia, rigors, decreased appetite, 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 modification although continuing therapy can lead to lethargy, asthenia and fatigue.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Body system	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)	Not known (cannot be estimated from the available data)
Infections and infestations				Pneumonia Herpes simplex[1]		
Blood and lymphatic system disorders[2]	Leukopenia	Thrombocytopenia Anaemia		Agranulocytosis Haemolytic anaemia	Idiopathic thrombocyto-penic purpura	Neutropenia
Immune system disorders				Autoimmune disorder Acute hypersensitivity reactions[3]	Sarcoidosis	Graft rejections†
Endocrine disorders				Hypothyroidism Hyperthyroidism Thyroid dysfunction		
Metabolism and nutrition disorders	Anorexia Nausea Inconsequential hypocalcemia		Dehydration Electrolyte imbalance	Diabetes mellitus Hyper-glycaemia	Hyper-triglyceridemia Hyperlipidaemia	
Psychiatric disorders			Depression Anxiety Mental status changes Confusional state Abnormal behaviour Nervousness Memory impairment Sleep disorder	Suicide Suicide attempt Suicidal ideation Mania		
Nervous system disorders	Headache	Dysgeusia	Neuropathy Dizziness Hypoesthesia	Coma Cerebrovascular accident	Encephalopathy	

			Paraesthesia Tremor Somnolence	Convulsions Transient erectile dysfunction		
Eye disorders			Visual disturbance Conjunctivitis	Ischemic retinopathy	Retinal artery thrombosis Optic neuropathy Retinal haemorrhage Retinal vein thrombosis Retinal exudates Retinopathy Papilledema	
Ear and labyrinth disorders			Vertigo			
Cardiac disorders		Arrhythmias[4] Palpitations Cyanosis		Cardiorespiratory arrest Myocardial infarction Congestive heart failure Pulmonary oedema		
Vascular disorders			Hypertension Hypotension	Vasculitis		
Respiratory, thoracic and mediastinal disorders				Dyspnoea Cough		
Gastrointestinal disorders	Diarrhoea	Vomiting Abdominal pain Nausea Dry mouth		Pancreatitis Intestinal hypermotility Constipation Dyspepsia Flatulence	Reactivation of peptic ulcer Gastrointestinal bleeding (non life threatening)	Ischaemic colitis Ulcerative colitis
Hepato-biliary disorders				Hepatic failure Hepatitis Hepatic dysfunction		
Skin and subcutaneous tissue disorders	Alopecia[5] Sweating increased		Psoriasis[6] Pruritus	Rash Dry skin Epistaxis Mucosal dryness Rhinorrhoea		
Musculoskeletal, connective tissue and bone disorders	Myalgia Arthralgia			Systemic lupus erythematosus Arthritis		
Renal and urinary disorders			Proteinuria Increased cell count in urine	Acute renal failure[7] Renal impairment		
General disorders and administration site conditions	Flu like illness Appetite decreased Pyrexia Rigors Fatigue	Chest pain Oedema			Injection site necrosis Injection site reaction	
Investigations		Weight loss	Increased ALT Increased transaminase Increased	Increased blood creatinine Increased blood urea Increased blood		

			blood alkaline phosphatase	bilirubin Increased blood uric acid Increased blood LDH		

[1](including exacerbations of herpes labialis)

[2]In myelosuppressed patients, thrombocytopenia and decreased haemoglobin occurred more frequently. Recovery of severe haematological deviations to pre-treatment levels usually occurred within seven to ten days after discontinuing Roferon-A treatment.

[3](e.g. urticaria, angioedema, bronchospasm and anaphylaxis)

[4]including atrioventricular block

[5](reversible upon discontinuation; increased hair loss may continue for several weeks after end of treatment)

[6]exacerbation of, or provocation of psoriasis

[7](mainly in cancer patients with renal disease)

† Identified in postmarketing experience

Rarely, alpha interferons including Roferon-A used alone or in combination with ribavirin, may be associated with pancytopenia, and very rarely, aplastic anaemia has been reported.

Neutralizing antibodies to interferons may form in some patients. In certain clinical conditions (cancer, systemic lupus erythematosus, herpes zoster) antibodies to human leukocyte interferon may also occur spontaneously in patients who have never received exogenous interferons. The clinical significance of the development of antibodies has not been fully clarified.

In clinical trials where lyophilised Roferon-A which had been stored at 25°C was used, neutralizing antibodies to Roferon-A have been detected in approximately one fifth of patients. In patients with hepatitis C, a trend for responding patients who develop neutralizing 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. The clinical significance of the development of antibodies has not been fully clarified.

No data on neutralizing antibodies yet exist from clinical trials in which lyophilized Roferon-A or Roferon-A solution for injection which is stored at 4°C has been used. In a mouse model, the relative immunogenicity of lyophilized Roferon-A increases with time when the material is stored at 25°C - no such increase in immunogenicity is observed when lyophilised Roferon-A is stored at 4°C, the recommended storage conditions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

4.9 Overdose

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

Patients who experience severe reactions to Roferon-A will usually recover within days after discontinuation of therapy, given appropriate supportive care. Coma has been observed in 0.4% of cancer patients in clinical trials.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, interferons, ATC Code L03AB04

Roferon-A has been shown to possess many of the activities of the so−called natural human alpha−interferon preparations. 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 neutralize viruses or eliminate virus infected cells. The essential mechanism for the antitumour action of Roferon-A is not yet known. However, several changes are described in human tumoural cells treated with Roferon-A: HT 29 cells show a significant reduction of DNA, RNA and protein synthesis. Roferon-A has been shown to exert antiproliferative activity against a variety of human tumours in vitro and to inhibit the growth of some human tumour xenografts in nude mice. A limited number of human tumour cell lines grown *in vivo* in immunocompromised nude mice has been tested for the susceptibility to Roferon-A. *In vivo* antiproliferative activity of Roferon-A has been studied on tumours including breast mucoid carcinoma, adenocarcinoma of the caecum, colon carcinoma and prostatic carcinoma. The degree of antiproliferative activity is variable.

Unlike other human proteins, many of the effects of interferon alfa−2a are partially or completely suppressed when it is tested in other animal species. However, significant antivaccinia virus activity was induced in rhesus monkeys pre-treated with interferon alfa-2a.

Clinical efficacy and safety

Hairy Cell Leukemia
The therapeutic efficacy of Roferon-A in the treatment of hairy cell leukemia has been demonstrated in a large trial of 218 patients, of whom 174 were evaluable for efficacy after 16−24 weeks of therapy. Response was observed in 88% of patients (complete response 33%, partial response 55%).

AIDS-related Kaposi's Sarcoma
The efficacy of Roferon-A in the treatment of Kaposi's sarcoma was assessed in 364 patients receiving of 3 to 54 million IU per day. Objective response rates were dose-related, ranging from 14% to 50%, with a daily dose of 36 million IU producing the best overall therapeutic benefit (13.3% complete response, 12.2% partial response). High baseline CD4 lymphocyte count was a favourable prognostic factor for response, with 46% of patients with a CD4 count > 400/mm^3 responding to Roferon-A. Response to Roferon-A therapy was the strongest prognostic factor for survival.

Chronic Myelogenous Leukemia (CML)
The efficacy of Roferon-A was assessed in 226 patients with chronic phase CML ,and compared with 109 patients receiving chemotherapy (hydroxyurea or busulfan). Both groups had favourable features at diagnosis (less than 10% blasts in the blood) and treatment was initiated with interferon within 6 months of diagnosis. Treatment of patients with CML in the chronic phase leads to the same proportion of patients (85-90%) achieving a hematologic response as treatment with the standard chemotherapy regimens. In addition patients treated with Roferon-A resulted in 8% complete cytogenetic response and 38% partial cytogenetic response versus 9% partial cytogenetic response during chemotherapy. Time to progression from the chronic phase of leukemia to an accelerated or a blastic phase was longer in the Roferon-A group (69 months) than in the conventional chemo-therapy group (46 months) ($p < 0.001$) as was median overall survival (72.8 months versus 54.5 months, $p=0.002$).

Cutaneous T-cell Lymphoma (CTCL)
The efficacy of Roferon-A was assessed in 169 patients with CTCL, the majority of whom (78%) were resistant to, or had relapsed on, standard therapy. Among the 85 patients evaluable, overall response to treatment was 58% (20% complete response, 38% partial response). Patients with all stages of disease responded to therapy. Median duration of

complete response from start of treatment was 22 months, with 94% of complete responders remaining in remission at 9 months.

Chronic Hepatitis B
The efficacy of Roferon-A in the treatment of chronic hepatitis B was assessed in trials involving over 900 patients. In the pivotal controlled study 238 patients were randomised into four groups: patients received either 2.5 million IU/m^2, 5.0 million IU/m^2, 10 million IU/m^2, 3 times per week of Roferon-A or no treatment. Treatment duration was 12−24 weeks depending on response, i.e., clearance of HBeAg and HBV DNA from serum. Patients were followed for up to 12 months after treatment was discontinued. There was a statistically significant difference in sustained response [clearance of hepatitis B e antigen (HBeAg) and hepatitis B viral DNA (HBV DNA)] between treated and untreated patients (37% versus 13%). Response differences between various dose groups did not reach statistical significance (33%, 34% and 43% for the 2.5, 5.0 and 10.0 million IU/m^2 groups). Serological and virological responses were associated with marked improvement in liver histology after 12 months of treatment free-follow up.

Chronic Hepatitis C
The efficacy of Roferon-A in the treatment of chronic hepatitis C has been assessed in 1701 patients, with 130 untreated or placebo treated controls. At recommended doses, Roferon-A induces complete biochemical response in up to 85% of patients, with response rates maintained for at least 6 months after treatment ranging from 11 to 44% depending on pre-treatment disease characteristics, IFN dose and treatment duration. Biochemical response to Roferon-A is associated with significant improvement of liver disease as shown by evaluation of pre-and post-liver biopsies. For those patients who have a sustained response 3−6 months after end of therapy, response has been reported to be maintained for up to 4 years.

The therapeutic efficacy of Interferon alfa-2a alone and in combination with ribavirin was compared in a double-blind randomised clinical trial in naive (previously untreated) and relapsed patients with virologically, biochemically and histologically documented chronic hepatitis C. Six months after end of treatment sustained biochemical and virological response as well as histological improvement were assessed.

A statistically significant 10-fold increase (from 4% to 43%; $p < 0.01$) in sustained virological and biochemical response was observed in relapsed patients. The favourable profile of the combination therapy was also reflected in the response rates relative to HCV genotype or baseline viral load. Although the sustained response rates in patients with HCV genotype-1 were lower than in the overall population (approx. 30% versus 0% in the monotherapy arm) the relative benefit of ribavirin in combination with interferon alfa-2a is particularly significant in this group of patients. In addition the histological improvement favoured the combination therapy.
Supportive favourable results from a small study in naïve patients were reported using interferon alfa-2a (3 million IU 3 times per week) with ribavirin.

For other information on pharmacodynamic properties please refer to the SmPC for Ribavirin.

Follicular Non-Hodgkin's lymphoma
The efficacy of Roferon-A in addition to cytotoxic chemotherapy (CHOP-like regimen of cyclophosphamide, vincristine, prednisone and doxorubicin) was assessed in 122 patients with clinically aggressive low-grade or intermediate-grade non-Hodgkin’s lymphoma and compared with 127 controls receiving the same chemotherapy regimen. The two regimens produced comparable objective responses, but the regimen including Roferon-A had a greater effect in prolonging the time to treatment failure ($p < 0.001$), the duration of complete response ($p < 0.003$).

Renal Cell Carcinoma
Combination with vinblastine
The efficacy of Roferon-A, given in combination with vinblastine, was compared with vinblastine alone. The combination of Roferon-A plus vinblastine is superior to vinblastine alone in the treatment of patients with locally advanced or metastatic renal cell carcinoma. Median survival was 67.8 weeks for the 79 patients receiving Roferon-A plus vinblastine and 37.8 weeks for the 81 patients treated with vinblastine ($p=0.0049$). Overall response rates were 16.5% for patients treated Roferon-A plus vinblastine and 2.5% for patients treated with vinblastine alone ($p=0.0025$).

Combination with bevacizumab (Avastin)

The pivotal phase III study compared bevacizumab in combination with interferon alfa-2a (N=327) to placebo plus interferon alfa-2a (N=322) as first-line therapy of nephrectomised patients with advanced and/or metastatic renal cell carcinoma.

Table 1: Efficacy results for study BO17705

Parameter (median value)	**Pbo + IFN N = 322**	**Bv + IFN N = 327**	**Hazard Ratio[α]**	**p-value**
Overall survival	21.3 mo.	23.3 mo.	0.91 (0.76 – 1.10)	p = 0.3360 [β]
Progression-free survival	5.4 mo.	10.2 mo.	0.63 (0.52 – 0.75)	p < 0.0001 [β]
Overall response rate [γ]	12.8%	31.4%	N/A	p < 0.0001 [δ]

α - determined with a 95% CI.
β - p-value was obtained using Log-Rank Test
γ - populations for reference are those patients with measurable disease at baseline [ITT N=289/306]
δ - p-value was obtained using $\chi 2$ Test

Surgically Resected Malignant Melanoma
The efficacy of Roferon-A in patients with primary cutaneous melanoma thicker than 1.5 mm and without clinically detectable node metastasis was assessed in a large randomised study involving 253 patients receiving Roferon-A at a dose of 3 million IU three times a week for 18 months, compared with 246 untreated controls. After a median follow-up of 4.4 years a significant extension of relapse-free interval (p=0.035) but no statistically significant difference in overall survival (p=0.059) in Roferon-A treated patients compared with controls have been shown. The overall treatment effect was a 25% reduction in the risk of relapse.

5.2 Pharmacokinetic properties

The serum concentrations of interferon alfa−2a reflected a large intersubject variation in both healthy volunteers and patients with disseminated cancer. The pharmacokinetics of Roferon-A in animals (monkey, dog and mouse) were similar to those seen in man. The pharmacokinetics of Roferon-A in man were linear over a 3 million to 198 million IU dose range. In healthy man, interferon alfa−2a exhibited an elimination half−life of 3.7−8.5 hours (mean: 5.1 hours), a volume of distribution at steady state of 0.223−0.748 l/kg (mean: 0.4 l/kg) and a total body clearance of 2.14−3.62 ml/min/kg (mean: 2.79 ml/min/kg) after a 36 million IU intravenous infusion. After intramuscular administration of 36 million IU, peak serum concentrations ranged from 1,500 to 2,580 pg/ml (mean: 2,020 pg/ml) at a mean time to peak of 3.8 hours, and after subcutaneous administration of 36 million IU from 1,250 to 2,320 pg/ml (mean: 1,730 pg/ml) at a mean time to peak of 7.3 hours.

The apparent fraction of the dose absorbed after intramuscular or subcutaneous injection is greater than 80%.

The pharmacokinetics of interferon alfa−2a after single intramuscular doses to patients with disseminated cancer and chronic hepatitis B were similar to those found in healthy volunteers. Dose−proportional increases in serum concentrations were observed after single doses up to 198 million IU. There were no changes in the distribution or elimination of interferon alfa−2a during twice daily (0.5−36 million IU), once daily (1−54 million IU), or three times weekly (1−136 million IU) dosing regimens up to 28 days of dosing. Renal catabolism is the major pathway for Roferon-A elimination. Biliary excretion and liver metabolism are considered to be minor pathways of elimination of Roferon-A.

Intramuscular administration of Roferon-A one or more times daily for up to 28 days to some patients with disseminated cancer resulted in peak plasma concentrations of two to four times greater than those seen after single doses. However, multiple dosing caused no changes in its distribution or elimination parameters during several dosage regimens studied.

For other information on pharmacokinetic properties please refer to the SmPC for Ribavirin.

5.3 Preclinical safety data

Because of species specificity of human interferon, only limited toxicological studies have been carried out with Roferon-A. The acute parenteral toxicity of Roferon-A has been studied in mice rats, rabbits and ferrets at doses up to 30 million IU/kg intravenously, and 500 million IU/kg intramuscularly. No treatment−related mortality was noted in any species studied given Roferon-A by any of the routes of administration. With doses greatly exceeding the recommended clinical dose no significant adverse effects were observed except for an abortifacient effect when administered to pregnant rhesus monkeys in the early to mid-foetal period and transient menstrual cycle irregularities including prolonged menstrual periods in non-pregnant monkeys. The relevance of these findings in man has not been established.

Mutagenic effects of Roferon-A have not been observed experimentally.

For other information on preclinical safety data please refer to the SmPC for Ribavirin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonium acetate
Sodium Chloride
Benzyl alcohol (10mg/1ml)
Polysorbate 80
Glacial Acetic acid
Sodium Hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 ml of solution for injection in pre-filled syringe (type I glass) with a plunger stopper (butyl rubber), a tip cap (butyl rubber), plunger rod (plastic), needle (stainless steel);pack sizes of 1, 5, 6, 12 and 30. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Any unused product or waste material, including needles and syringes, should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Roche Products Limited

6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
UK

8 MARKETING AUTHORISATION NUMBER

PA 50/68/21

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 October 1999

Date of last renewal: 22 July 2009

10 DATE OF REVISION OF THE TEXT

March 2015