

## Summary of the clinical-pharmacological assessment

### **Roferon A<sup>®</sup> & Roferon A EasyJect<sup>®</sup> in combination therapy with Ribavirin for the treatment of patients with Chronic Hepatitis C (CHC)**

Name product : *Roferon A<sup>®</sup> & Roferon A EasyJect<sup>®</sup>*  
Active substance : interferon alfa-2a  
Pharmaceutical form : solution for injection, 3, 4.5, 6, & 9 million IE/1ml and 18 million IE/3ml  
(Roferon A EasyJect : 3, 4.5, 6, & 9 million IE/0.5ml )  
Marketing authorisation holder : Roche Nederland/NL  
Date : 11 May 2001/rev 1 31 May 2001

## Summary of the clinical-pharmacological assessment

### Roferon A® & Roferon A EasyJect® in combination therapy with Ribavirin for the treatment of patients with Chronic Hepatitis C (CHC)

#### Introduction

Roferon-A , solutions for injection 3, 4.5, 6, 9 and 18 MIU have been approved in The Netherlands on 14-3-1996. Roferon-A Easyject solutions for injection 3, 4.5, 6, 9 have been approved in The Netherlands 24-8-99. Roferon-A 18, solution for injection 18 MIU/0.6 ml has been approved 28-3-2000. The first submissions for Roferon-A were made via the concertation procedure. After 1-1-1995 these products were converted into the Mutual Recognition Procedure. Based on the agreements made during the concertation procedure, in the Mutual Recognition Procedure UK was acting as RMS for the chemical-pharmaceutical assessment and The Netherlands for the assessment of the clinical data and the SPC.

The Marketing Authorisation Holder (MAH) is Roche Nederland. The products are approved in all EU countries.

The last revision in the SPC, with regard to the Section 4.1 was made 17 December 1998 were the CPMP issued a positive opinion for an extension of indications.

The approved indications in the SPC of Roferon-A at that time were:

- 1) Hairy cell leukemia.
- 2) AIDS patients with progressive, asymptomatic Kaposi's sarcoma who have a CD4 count  $> 250/\text{mm}^3$ . AIDS patients with CD4 counts  $< 250/\text{mm}^3$ , or those with a history of opportunistic infections or constitutional symptoms, are unlikely to respond to Roferon-A/Roceron-A/Roféron-A therapy and therefore should not be treated (see section 4.2 posology and method of administration).
- 3) Chronic phase Philadelphia-chromosome positive chronic myelogenous leukemia. Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A can be considered as a treatment with a curative potential in this indication.
- 4) Cutaneous T-cell lymphoma. Interferon alfa-2a (Roferon-A/Roceron-A/Roféron-A ) may be active in patients who have progressive disease and who are refractory to, or unsuitable for, conventional therapy.
- 5) 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.
- 6) 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.
- 7) Follicular non-Hodgkin's lymphoma.

- 8) Advanced renal cell carcinoma.
- 9) 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.

In this report a change in the Section Therapeutic indications in the SPC will be discussed. This was a type II variation in the Mutual Recognition Procedure with Procedure number NL/H/28/6-15/W07-08.

#### **Variation procedure NL/H/28/6-15/W07-08**

The MAH submitted a type II variation to extend the indications in the RMS and all CMSs. This procedure started 22 December 1999. The RMS sent out a preliminary variation assessment report to all CMSs and a list with questions including also the comments from other Member States was sent to the MAH.

The procedure restarted 29-4-00 with the circulation of a final variation assessment report and the variation was approved by all Member States 29 May 2000.

After approval the revised SPC included the following additional statement in the Section therapeutic indications (new text in bold):

"Adult patients with histologically proven chronic hepatitis C who are positive for HCV antibodies or HCVRNA 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 the case of intolerance or contraindication to ribavirin."**

#### **Scientific assessment**

The state of the art of treatment of patients with Chronic Hepatitis C is the combination therapy of interferon (INF) with ribavirin (see references <sup>i,ii,iii,iv,v,vi,vii,viii,ix</sup>). The efficacy of interferon in the treatment of hepatitis C is enhanced when combined with ribavirin. Interferon should be given alone mainly in case of intolerance or contraindication to ribavirin. A CPMP scientific Opinion for combination therapy with ribavirin plus interferon alfa-2b was made public in February 1999.

In line with the state of the art, the Marketing Authorisation Holder for interferon alfa-2a (Roferon A<sup>®</sup> & Roferon A EasyJect<sup>®</sup>) has sought the update of the treatment recommendations for CHC with interferon alfa-2a. Three small trials and extensive literature review plus justification of the studied dosage of INF were provided to support the claim that the use of *interferon alfa-2a in the treatment of hepatitis C is enhanced when combined with ribavirin*. The state of the art scientific criteria were applied to the assessment of the latter claim together with claimed specific posology based on the clinical experience with Roferon A.

The efficacy and safety of Roferon<sup>®</sup>-A in combination with ribavirin for the treatment of CHC has been documented in three multiple dose therapeutic trials with in total 213 patients (relapsed, naive and responders). Ninety-eight received Roferon<sup>®</sup>-A with ribavirin.

Based on the abundant clinical experience with doses of 3 to 6 MIU thrice weekly Roferon<sup>®</sup>-A in CHC patients as being safe and the increased knowledge from literature obtained from quantitative measurements of HCV RNA indicating that early fall of HCV is dose dependent one may accept the used dose in these studies as a reasonable choice fitting the range of accepted dose range. Dose response studies were therefore not considered.

The therapeutic efficacy of interferon alfa-2a (4.5 MIU 3 times per week) alone and in combination with ribavirin (1000 mg daily) was compared in a small double-blind randomised (French) clinical trial with relapsed patients with virologically, biochemically and histologically documented chronic hepatitis C (unpublished report- in company file, 1999). The primary efficacy variable was complete and sustained response (SR), defined as the normalisation of ALT at the end of treatment and monthly up to the end of follow-up period (at least 6 months after treatment), as well as a negative test for HCV-RNA at the end of treatment and the end of the follow-up period whereas the secondary endpoint was an improvement in liver histology.

A statistically significant 10-fold (from 4% to 43%, ITT analysis) increase in sustained virological and biochemical response was observed in the relapsed patients. See the following table.

	<b>Roferon<sup>®</sup> - A/Placebo N=50</b>	<b>Roferon<sup>®</sup> - A/RVN N=49</b>	<b>p value</b>
<b>Rates of Complete and Sustained Response in Relapsed Patients</b>			
Complete and Sustained Response (LOCF, ITT population)	2 (4%)	21 (43%)	<0.01
SR According baseline (missing data ignored)			
Genotype 1	0/24 (0%)	7/25 (28%)	
Genotype non 1	2/26 (8%)	14/24 (58%)	
Viral load $\leq$ 100,000	1/10	7/10	
Viral load > 100,000	1/40 (3%)	14/39 (36%)	
<b>Histological Improvement 6 months after the end of treatment</b>			
<b>Improvement</b>	19 (45%)	26 (68%)	<0.05
<b>No Change</b>	12 (29%)	7 (18%)	
<b>Worsening</b>	11 (26%)	5 (13%)	

The favourable profile of the combination therapy was also reflected in the response rates according to baseline HCV genotype or viral load. Although the sustained response rate in patients with HCV genotype-1 was somewhat lower (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. Furthermore, one other supportive small randomised study in either non-responder (n=26) or relapsed patients (n=27) conducted in Norway was also provided (Bell H et al, 1999<sup>x</sup>). Dose regimens used and the duration of treatment and follow-up period were comparable with those in the pivotal study. However, no control biopsies were performed in this study to allow histological improvement assessment. There was also an imbalance in the distribution of genotypes over the groups and the number of patients was too small to allow robust conclusions.

Supportive favourable results in naïve patients were derived from a randomised controlled trial conducted in Taiwan between 1992 and 1995 in 60 consecutive previously untreated patients with CHC (Lai M-Y et al, 1996<sup>xi</sup>). Nineteen patients were randomised to receive Roferon<sup>®</sup>-A alone, 21 to the combination and 20 to the untreated control arm. The patients received 3 MIU of Roferon<sup>®</sup>-A t.i.w alone or in combination with ribavirin 1200 mg in 2 daily divided doses for 6 months. Also in this study the improvement of the response rate with combination treatment was consistent with the findings in the pivotal study in relapsed patients. Rates of Complete and Sustained Response Naïve Patients at 24 weeks was 10/21 (48%) with combination therapy vs. 1/19 (6%) with INF monotherapy.

In addition the histological improvement of naïve and relapsed patients favoured also the combination therapy based on control biopsy assessments performed for 70% and 80% of the patients in the Taiwan and French studies respectively.

These findings are consistent with data described for combination therapy with Interferon- $\alpha$ -2b plus ribavirin in CHC patients (see e.g. ref. 1-3).

In conclusion, there is sufficient evidence that the use of interferon alfa-2a in the treatment of hepatitis C is enhanced when combined with ribavirin at the tested doses. However, the results may not be equally robust or well documented in provided three studies in all relevant subgroups of patients with CHC. The response of the company to raised questions especially with regard to subgroups covered and dosage range during the assessment was satisfactory. In support, it can be argued that the concept and the benefit derived from combination therapy with INF and ribavirin are well established (state of the art) and need to be implemented for all INFs on the market. The available data suggest that the safety profiles of Interferon- $\alpha$ -2b and Interferon- $\alpha$ -2a are similar when used in combination with ribavirin at the specified doses in their respective SmPCs. The adverse events for Roferon-A and ribavirin were comparable with the side effects already known from both individual components.

In the light of available data the indication for Interferon- $\alpha$ -2a in CHC was updated to read as follows:

Roferon-A/Roceron-A/Roféron-A is indicated for the treatment of 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/Roceron-A/Roféron-A should be given alone mainly in case of intolerance or contraindication to ribavirin.*

Interferon- $\alpha$ -2a for relapsed patients is given in combination with ribavirin for adult patients with chronic hepatitis C who have previously responded to Interferon- $\alpha$ -2a monotherapy, but who have relapsed after treatment was stopped. The dosage for such patients was set at 4.5 MIU 3 times per week by subcutaneous or intramuscular injection for a period of 6 months.

For naïve patients the dosage was set at 3 to 4.5 MIU 3 times per week by subcutaneous or intramuscular 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, are infected with genotype 1 and have high viral load (pretreatment determinations).

For further details see the SmPC text. (The SPC of Roferon-A 3 MIU is attached as example the SPC's of other strengths are similar.)

## References

<sup>i</sup> Mchutchison J.G., Gordon S.C., Schiff E.R. et al. *Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C*. N Engl J Med. 1998; 339 (21): 1485-1492.

<sup>ii</sup> Davis G.L., Esteban-Mur R., Rustgi V. et al. *Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C*. N Engl J Med. 1998; 339 (21): 1493-1499.

<sup>iii</sup> Reichard O., Norkrans G., Fryden A. et al. *Randomised, double-blind, placebo-controlled trial of interferon Alpha-2b with and without ribavirin for chronic hepatitis C*. Lancet 1998; 351: 83-87.

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- <sup>iv</sup> Poynard T., Marcellin P., Lee SS. et al. *Randomised trial of interferon Alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon Alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus*. Lancet 1998; 352: 1426-1432.
- <sup>v</sup> Brown JL. *Efficacy of combined Interferon and ribavirin for the treatment of hepatitis C*. Lancet 1998; 351: 78-79. (Commentary)
- <sup>vi</sup> Liang TJ. *Combination therapy for hepatitis C infection*. N Engl J Med 1998; 339 (21): 1549-50. (Editorial)
- <sup>vii</sup> Schafer DF & Sorelli MF. *Conquering Hepatitis C, Step by Step*. N Engl J Med. 2000; 343 (23): 1723-1724. (Editorial)
- <sup>viii</sup> Lin OS, Keeffe EB. *CURRENT TREATMENT STRATEGIES FOR CHRONIC HEPATITIS B AND C*. Annu Rev Med 2001; 52: 29-49. (Review)
- <sup>ix</sup> Boyer N, Marcellin P. *Pathogenesis, diagnosis and management of hepatitis C*. J Hepatol 2000; 32 (1 Suppl): 98-112. (Review)
- <sup>x</sup> Bell H, Hellum K, Harthug S, Myrvang B, Ritland S, Maeland A, von der Lippe B, Bjoro K, Skaug K, Gutigard BG, Raknerud N, Simmonds P and the Construct Group. *Treatment with Interferon-alpha2a alone or Interferon-alpha2a plus Ribavirin in patients with Chronic Hepatitis C previously treated with Interferon-alpha2a*. Scand J Gastroenterol 1999 (2); 194-198.
- <sup>xi</sup> Lai M-Y, Kao J-H, Yang P-M, Wang J-T, Chen P-J, Chan K-W, Chu J-S and Chen D-S (). *Long-Term Efficacy of Ribavirin plus Interferon-Alfa in the Treatment of Chronic Hepatitis C*. Gastroenterol 1996; 111: 1307-1312.

## 1. NAME OF MEDICINAL PRODUCT

Roferon-A 3 MIU/1 ml /Roceron-A 3 MIU/1 ml /Roféron-A 3 MIU/1 ml  
Solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Roferon-A/Roceron-A/Roféron-A is supplied in vials as a ready-to-use solution for injection. Each vial contains 3 Million International Units interferon alfa-2a\* per millilitre (3 MIU/1 ml).

\* Contains volume overages of 10% and manufacturing overages.

## 3. PHARMACEUTICAL FORM

Vials containing solution for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Roferon-A/Roceron-A/Roféron-A is indicated for the treatment of:

- 1) Hairy cell leukemia.
- 2) AIDS patients with progressive, asymptomatic Kaposi's sarcoma who have a CD4 count > 250/mm<sup>3</sup>. AIDS patients with CD4 counts < 250/mm<sup>3</sup>, or those with a history of opportunistic infections or constitutional symptoms, are unlikely to respond to Roferon-A/Roceron-A/Roféron-A therapy and therefore should not be treated (see section 4.2 posology and method of administration).
- 3) Chronic phase Philadelphia-chromosome positive chronic myelogenous leukemia. Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A can be considered as a treatment with a curative potential in this indication.
- 4) Cutaneous T-cell lymphoma. Interferon alfa-2a (Roferon-A/Roceron-A/Roféron-A ) may be active in patients who have progressive disease and who are refractory to, or unsuitable for, conventional therapy.
- 5) 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.
- 6) 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/Roceron-A/Roféron-A should be given alone mainly in case of intolerance or contraindication to ribavirin.

- 7) Follicular non-Hodgkin's lymphoma.
- 8) Advanced renal cell carcinoma.

- 9) 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

##### 1. HAIRY CELL LEUKEMIA

###### Initial dosage:

Three million IU daily, given by subcutaneous or intramuscular 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 or intramuscular 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/Roceron-A/Roféron-A treatment for hairy cell leukemia has not been determined.

###### Note:

Subcutaneous administration is recommended for thrombocytopenic patients (platelet count less than  $50 \times 10^9/l$ ) or patients at risk of bleeding.

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

##### 2. AIDS-RELATED KAPOSI'S SARCOMA

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

Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A with reverse transcriptase inhibitors.

###### Initial dosage:

Roferon-A/Roceron-A/Roféron-A should be given by subcutaneous or intramuscular 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/Roceron-A/Roféron-A should be given by subcutaneous or intramuscular 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/Roceron-A/Roféron-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/Roceron-A/Roféron-A treatment for AIDS-related Kaposi's sarcoma has not been determined.

**Note:**

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

**3. CHRONIC MYELOGENOUS LEUKEMIA**

Roferon-A/Roceron-A/Roféron-A is indicated for the treatment of patients with chronic phase Philadelphia-chromosome positive chronic myelogenous leukemia. Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A produces hematological remissions in 60% of patients with chronic phase CML, independent of prior treatment. Two thirds of these patients have complete hematological 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/Roceron-A/Roféron-A can be considered as a treatment with a curative potential in this indication.

**Dosage:**

It is recommended that Roferon-A/Roceron-A/Roféron-A should be given by subcutaneous or intramuscular 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 hematological parameters. Responding patients should be treated until complete hematological response is achieved or for a maximum of 18 months. All patients with complete hematologic responses should continue treatment with 9 million IU daily (optimum) or 9 million IU three times a week (minimum) in order to achieve a cytogenetic response in the shortest possible time. The optimal duration of Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A in children with CML has not yet been established.

#### **4. CUTANEOUS T-CELL LYMPHOMA (CTCL)**

Interferon alfa-2a (Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A should be given by subcutaneous or intramuscular 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/Roceron-A/Roféron-A should be given by subcutaneous or intramuscular 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/Roceron-A/Roféron-A treatment for cutaneous T-cell lymphoma has not been determined.

##### **Warning:**

Objective tumor 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.

#### **5. CHRONIC HEPATITIS B**

Roferon-A/Roceron-A/Roféron-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<sup>2</sup> 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/m<sup>2</sup> 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/Roceron-A/Roféron-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/Roceron-A/Roféron-A : 4.5 MIU 3 times per week by subcutaneous or intramuscular 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/Roceron-A/Roféron-A should be given alone mainly in case of intolerance or contraindication to ribavirin.

#### Dosage:

Roferon-A/Roceron-A/Roféron-A : 3 to 4.5 MIU 3 times per week by subcutaneous or intramuscular 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/Roceron-A/Roféron-A monotherapy should be given mainly in case of intolerance or contraindication to ribavirin.

#### Initial dosage:

Roferon-A/Roceron-A/Roféron-A should be administered at a dose of 3 to 6 million IU by subcutaneous or intramuscular 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/Roceron-A/Roféron-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/Roceron-A/Roféron-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/Roceron-A/Roféron-A alone do so within four months of the end of treatment.

**7. FOLLICULAR NON-HODGKINS LYMPHOMA**

Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-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<sup>2</sup> given subcutaneously or intramuscularly from day 22 to day 26 of each 28-day cycle.

**8. ADVANCED RENAL CELL CARCINOMA**

Therapy with Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A should be given by subcutaneous or intramuscular 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/Roceron-A/Roféron-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.

**9. SURGICALLY RESECTED MALIGNANT MELANOMA.**

Adjuvant therapy with a low dose of Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A should be administered subcutaneously or intramuscularly 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/Roceron-A/Roféron-A is contraindicated in patients with:

- 1) A history of hypersensitivity to recombinant interferon alfa-2a or any component of the preparation,
- 2) 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/Roceron-A/Roféron-A may exacerbate pre-existing cardiac conditions,
- 3) Severe renal, hepatic or myeloid dysfunction,
- 4) Uncontrolled seizure disorders and/or compromised central nervous system function (see section 4.4.),
- 5) Chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis of the liver,
- 6) Chronic hepatitis who are being or have recently been treated with immunosuppressive agents,
- 7) Benzyl alcohol which is an excipient in Roferon-A/Roceron-A/Roféron-A solution for injection has on rare occasions been associated with potentially fatal toxicities in neonates. Therefore, Roferon-A/Roceron-A/Roféron-A solution for injection should not be used in the neonatal period.

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 Special Precautions for Use

Roferon-A/Roceron-A/Roféron-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.

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

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 in these patients develops a determination of autoimmune antibodies should be considered. If necessary treatment should be discontinued.

Careful periodic neuropsychiatric monitoring of all patients is recommended. Suicidal behaviour has been observed rarely in patients receiving Roferon-A/Roceron-A/Roféron-A. Therapy should be discontinued in patients exhibiting suicidal behaviour.

Extreme caution should be exercised when administering Roferon-A/Roceron-A/Roféron-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, hemoglobin 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/Roceron-A/Roféron-A treatment, both prior to therapy and at appropriate periods during therapy.

In transplant patients (e.g., kidney or bone marrow transplant) therapeutic immunosuppression may be weakened because interferons also exert an immunostimulatory action.

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

In rare cases, severe hepatic dysfunction and liver failure have been reported after treatment with alfa interferon.

Hyperglycemia has been observed rarely in patients treated with Roferon-A/Roceron-A/Roféron-A. All patients who develop symptoms of hyperglycemia should have their blood glucose measured and followed-up accordingly. Patients with diabetes mellitus may require adjustment of their antidiabetic regimen.

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, hemolytic anemia, thyroid dysfunction and lupus erythematosus syndrome have been observed rarely in patients receiving Roferon-A/Roceron-A/Roféron-A. 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/Roceron-A/Roféron-A in children is not recommended as the safety and effectiveness of Roferon-A/Roceron-A/Roféron-A in children have not been established.

Efficacy in patients with chronic hepatitis B or C who are on hemodialysis or have hemophilia or are coinfecting with human immunodeficiency virus has not been demonstrated.

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.

#### **4.5 Interactions with Other Medicinal Products and Other Forms of Interaction**

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

Alfa-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/Roceron-A/Roféron-A has been reported to reduce the clearance of theophylline.

As Roferon-A/Roceron-A/Roféron-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.

#### **4.6 Use During Pregnancy and Lactation**

Men and women receiving Roferon-A/Roceron-A/Roféron-A should practise effective contraception. In pregnancy, Roferon-A/Roceron-A/Roféron-A should be administered only if the benefit to the woman justifies the potential risk to the fetus. Although animal tests do not indicate that Roferon-A/Roceron-A/Roféron-A is a teratogen, harm to the fetus 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-fetal period, an abortifacient effect was observed.

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.

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.

#### 4.7 Effects on Ability to Drive and Use Machines

Depending on dose and schedule as well as the sensitivity of the individual patient, Roferon-A/Roceron-A/Roféron-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

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 to 2 weeks after the end of therapy.

**General symptoms** The majority of the patients experienced flu-like symptoms such as 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 although continuing therapy can lead to lethargy, weakness and fatigue.

**Gastrointestinal tract:** About two thirds of cancer patients experienced anorexia and one half nausea. Emesis, taste alterations, mouth dryness, weight loss, diarrhea and mild or moderate abdominal pain were less frequently observed. Constipation, flatulence, hypermotility or heartburn occurred rarely, and reactivation of peptic ulcer and non-life-threatening gastrointestinal bleeding have been reported in isolated cases.

**Alterations of hepatic function** shown by an elevation particularly of ALT, but also of alkaline phosphatase, LDH and bilirubin have been observed and generally did not require dose adjustment. In rare cases hepatitis was reported. In hepatitis B patients, changes in transaminases usually signal an improvement in the clinical state of the patient.

**Central nervous system:** Dizziness, vertigo, visual disturbances, decreased mental status, forgetfulness, depression, drowsiness, confusion, behavioural disturbances such as anxiety and nervousness, and sleep disturbances were uncommon. Suicidal behaviour, severe somnolence, convulsions, coma, cerebrovascular adverse events, transient impotence and ischemic retinopathy were rare complications.

**Peripheral nervous system:** Paresthesia, numbness, neuropathy, itching and tremor occasionally occurred.

**Cardiovascular and pulmonary systems** Disorders were seen in about one fifth of cancer patients and consisted of transient hypotensive and hypertensive episodes, edema, cyanosis, arrhythmias, palpitations and chest pain. Coughing and mild dyspnea were rarely observed. Rare cases of pulmonary edema, pneumonia, congestive heart failure, cardiorespiratory arrest and myocardial infarction have been reported. Cardiovascular problems are very rarely seen in patients with hepatitis B.

**Skin, mucous membranes and adnexa:** Re-exacerbation of herpes labialis, rash, pruritus, dryness of skin and mucous membranes, rhinorrhea and epistaxis were reported rarely. Mild to moderate alopecia occurred in up to one fifth of patients, but this was reversible on discontinuation of treatment. Increased hair loss may continue for several weeks after treatment ends.

**Renal and urinary system:** In rare instances, decreased renal function has occurred. Electrolyte disturbances have been seen, generally in association with anorexia or dehydration. Disorders consisted primarily of proteinuria and increased cell count in sediment. Elevation of BUN, serum creatinine and uric acid has been observed in rare cases. Rare cases of acute renal failure have been reported, mainly in cancer patients with renal disease and/or nephrotoxic comedications as concomitant risk factors.

**Hematopoietic system:** Transient leukopenia occurred variably in about one third to over one half of the patients, but rarely required restriction of dosage. In non-myelosuppressed patients, thrombocytopenia was less frequently seen, and decrease of hemoglobin and hematocrit occurred rarely. In myelosuppressed patients, thrombocytopenia and decreased hemoglobin occurred more frequently. Recovery of severe hematological deviations to pre-treatment levels usually occurred within seven to ten days after discontinuing Roferon-A/Roceron-A/Roféron-A treatment.

**Endocrine Disorders:** Inconsequential hypocalcemia was reported in about one half of the patients. Hyperglycemia has been observed rarely in patients treated with Roferon-A/Roceron-A/Roféron-A .

Reactions at injection sites have occurred in patients.

**Anti-Interferon Antibodies:** Neutralizing 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 leukocyte interferon may also occur spontaneously in patients who have never received exogenous interferons.

In clinical trials where lyophilised Roferon-A/Roceron-A/Roféron-A which had been stored at 25 C was used, neutralizing antibodies to Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-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/Roceron-A/Roféron-A or Roferon-A/Roceron-A/Roféron-A solution for injection which is stored at 4 C has been used. In a mouse model, the relative immunogenicity of lyophilized Roferon-A/Roceron-A/Roféron-A increases with time when the material is stored at 25 C - no such increase in immunogenicity is observed when lyophilised Roferon-A/Roceron-A/Roféron-A is stored at 4 C, the recommended storage conditions.

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.

#### 4.9 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/Roceron-A/Roféron-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 classification: Immunostimulating Agent/Cytokine  
ATC Code L03AA04

Roferon-A/Roceron-A/Roféron-A has been shown to possess many of the activities of the so-called natural human alfa-interferon preparations. Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A is not yet known. However, several changes are described in human tumoural cells treated with Roferon-A/Roceron-A/Roféron-A: HT 29 cells show a significant reduction of DNA, RNA and protein synthesis. Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A. *In vivo* antiproliferative activity of Roferon-A/Roceron-A/Roféron-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.

#### Chronic Hepatitis C:

The therapeutic efficacy of Interferon alfa-2a alone and in combination with ribavirin was compared in a double-blind randomised clinical trial in naïve (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 ~~also~~ the combination therapy.

Supportive favourable results from a small study in naïve patients were reported using interferon alfa-2a (3 MIU 3 times per week) with ribavirin. For other information on pharmacodynamic properties please refer to the SmPC for Ribavirin.

### 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/Roceron-A/Roféron-A in animals (monkey, dog and mouse) were similar to those seen in man. The pharmacokinetics of Roferon-A/Roceron-A/Roféron-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 1500 to 2580 pg/ml (mean: 2020 pg/ml) at a mean time to peak of 3.8 hours, and after subcutaneous administration of 36 million IU from 1250 to 2320 pg/ml (mean: 1730 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/Roceron-A/Roféron-A elimination. Biliary excretion and liver metabolism are considered to be minor pathways of elimination of Roferon-A/Roceron-A/Roféron-A .

Intramuscular administration of Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-A . The acute parenteral toxicity of Roferon-A/Roceron-A/Roféron-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/Roceron-A/Roféron-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/Roceron-A/Roféron-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  
Polysorbate 80  
Acetic acid  
Sodium Hydroxide  
Water for Injection

### 6.2 Incompatibilities

None observed

### 6.3 Shelf-Life

2 years (at 2 – 8 C).

### 6.4 Special Precautions for Storage

Store vials between +2 and +8 C. Protect from light. Do not freeze.

The 3 MIU/1ml solution for injection is for single dose use.

#### **6.5 Nature and Contents of Container**

- Vial 2 ml (flint glass), butyl rubber stopper laminated with FPE, aluminium cap. Each vial contains 1 ml of solution for injection.
- An injection kit (1 syringe 2 ml, 1 needle for i.m. injection, 1 needle for s.c. injection) may be supplied with the product.

#### **6.6 Instructions for Use/Handling**

Plastic syringes are recommended for administration of Roferon-A/Roceron-A/Roféron-A solution for injection.

#### **7. MARKETING AUTHORISATION HOLDER**

#### **8. MARKETING AUTHORISATION NUMBER**

#### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

#### **10. DATE OF REVISION OF THE TEXT**