Reiferon Retard®

Not for use in neonates and infants, the product contains benzyl alcohol.

Pegylated Hansenula-derived Recombinant Interferon alfa-2a for subcutaneous administration.
Composition:

Pegylated Hansenula-derived recombinant interferon alfa-2a	160 µg

Pharmaceutical form:
Pegylated interferon alfa-2a is supplied in vials.
Each 1.2 ml/vial containing 160 µg pegylated Hansenula-derived liquid interferon.
Pharmacological action:
Recombinant interferon alfa-2a has an **antiviral activity,** besides it possesses **anti-proliferative & immune-regulatory** properties. Studies have shown interferon to have benefit in infections with Hepatitis B virus, Hepatitis C virus besides many others.
Pharmacokinetics
The pharmacokinetics of Reiferon Retard® was assessed giving a single subcutaneous (SC) dose of 1.2 ml to deliver at least 1 ml of the product which showed a significant inter-patient variability. $T_{1/2}$ is 1 day. Maximal plasma concentration (Cmax) ranges from 1249-1926 pg/ml. The elimination half-life ($T_{1/2}\lambda z$) ranges from 19.44-61.68 hours. Total elimination rate constant (K) ranges from 0.269-0.855 day $^{-1}$. The dose normalized (AUC_{∞}) ranges from 2.44 x10^{1}-3.98 x10^{1} pg.day /ml.
Indications:
Chronic hepatitis C:

Reiferon Retard® is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis.

The optimal way to use Reiferon Retard® in patients with chronic hepatitis C is in combination with ribavirin. The combination of Reiferon Retard® and ribavirin is indicated in naive patients and patients who have failed previous treatment with interferon alpha (pegylated or non-pegylated) alone or in combination with Ribavirin. Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.

Dosage and administration:

Chronic hepatitis C:
The recommended dose of Reiferon Retard® when used in combination with ribavirin is one vial (160 µg) once weekly or as indicated by the prescribing physician. The recommended dose of ribavirin is demonstrated in Table 1.

The daily dose of ribavirin is 800 mg to 1200 mg administered orally in two divided doses. The dose should be individualized for the patient depending on baseline disease characteristics (e.g. genotype), response to therapy and tolerability of the regimen. Since absorption of ribavirin increases when administered with a meal, patients are advised to take ribavirin with food.

Table 1: Ribavirin Dosing Recommendations

Genotype	Body weight (kg)	Ribavirin Dose (mg/day)
Genotype 1, 4	< 75	1000
Genotype 1, 4	≥ 75	1200

Clinical efficacy & Safety:
Clinical pharmacology trials in treatment of naive patients:

One hundred (100) chronic hepatitis C Egyptian patients divided according to the degree of fibrosis on liver biopsy into group A (including F1 and F2) patients and group B (including F3 and F4). Patients received a fixed weekly dose of 160 µg of Reiferon Retard® interferon in combination with ribavirin in standard with adjusted dosage and were followed up by PCR after 3, 6, 12 and 18 months. End of treatment response (ETR), sustained virological response (SVR), possible side effects, discontinuation of the drug, and concomitant use of cytokines were reported. At 48 weeks the overall ETR rate was 64% with 73% and 40% for group A and B respectively, and SVR at 72 weeks revealed an overall response rate of 56% viral clearance with 69% and 22% for group A and B respectively. There were notably minimal haematological complications.

An open labeled trial, where **four hundred & eighty (480) chronic hepatitis C Egyptian patients** were evaluated, receiving a weekly fixed dose of 160 µg Reiferon Retard® and ribavirin in a dose of 11-13mg/kg for 48 weeks. Patients underwent consistent clinic, biochemical, and virological evaluations during treatment. PCR was performed at 12, 48 and 72 weeks from starting treatment. The early virological response at week 12 was 80% (95% CI: 76.42-83.58%). End of treatment response at week 48 was 75% (95% CI: 71.13-78.87%). The primary end point of sustained virological response was 60% (95% CI: 55.62-64.38%) at 72 weeks. Treatment was found to be tolerable and safe. None of the patients have stopped treatment due to adverse events.

One hundred and seven (107) chronic hepatitis C patients genotype 4 were involved in this study. Liver biopsy was performed in all patients. All patients received fixed weekly dose of 160 µg Reiferon Retard® in combination with ribavirin in standard and adjusted doses. Serum HCV RNA was assessed by a real time sensitive PCR at 4, 12, 48 and 72 weeks from the start of therapy. Early virological responders (EVR) completed a 48 week course of treatment.
Overall sustained virological response (SVR) was 60.7%. The SVR in patients with rapid virological response (RVR) was significantly higher (91.7%) than patients with complete EVR (67.74%) (p=0.033) and partial EVR (56.14%) (p=0.003). SVR was also higher significantly in patients with low degree of liver fibrosis by Metavir score (F1 & F2) (67.57%) compared to those with high degree (F3 & F4) (45.45%) (p=0.017). The baseline viral load had no impact on SVR in our series. No serious adverse events were reported in this study.

One hundred and twenty four (124) chronic hepatitis C patients genotype 4 were involved in this study. Liver biopsy was performed in all patients. Patients were randomized into 2 groups: Group I which included 63 patients who received fixed weekly dose of 160 µg of Reiferon Retard® in combination with ribavirin in standard and adjusted doses. Group II included 61 patients who received amantadine sulfate 100 mg twice daily orally in addition to the regimen of group I patients. Serum HCV RNA was assessed by a real time sensitive PCR at 4, 12, 48 and 72 weeks from the start of therapy. Early virological responders (EVR) completed a 48 week course of treatment. Sustained virological response (SVR) was (58.73%) in group I and (63.93%) in group II and this difference was statistically insignificant (p=0.552). The SVR was significantly higher in patients with low degree of liver fibrosis by Metavir score (F1 & F2) in groups I and II compared to those with high degree of liver fibrosis (F3 & F4) (69.77% versus 33%, p=0.004 in group I; 75% versus 45%, p=0.026 in group II). The distribution of patients with low degree of liver fibrosis was statistically indifferent in both groups (66.66% in group I, 65.57% in group II; p=0.898).SVR was significantly higher in patients who achieved rapid virological response (RVR) than those who could not achieve RVR in both groups (82.3% versus 50%, p=0.006 in group I; 91.67% versus 57.14%, p=0.026 in group II). The baseline viral load had no impact on SVR in both groups. No serious adverse events were reported in this study.

Two hundred (200) chronic hepatitis C naive Egyptian patients were enrolled. Patients received a fixed weekly dose of 160 µg Reiferon Retard® in combination with ribavirin in a dose ranging from 11-13 mg/kg and were followed up by PCR after 3, 6,12 and 18 months. End of treatment response (ETR), sustained virological response (SVR), reported side effects, and concomitant use of cytokines were reported. At 3 months the overall response was 73 %. At 6 months the overall response was 67.8% (130/189 patients). At 12 months the overall ETR rate was 60.3% and SVR at 18 months revealed an overall response rate of 53.4% viral clearance.

One hundred and two (102) chronic hepatitis C patients genotype 4 were treated with Reiferon Retard® (160µg/week) Plus dose adjusted ribavirin (according to body weight 13mg/kg) for 48 weeks. Early virological response (EVR), End of treatment response (ETR), Sustained virological response (SVR), possible side effects and discontinuation of the drug were reported. At week 12, early virological response was achieved in 76.47% of patients (78 out of 102 patients). Undetectable HCV RNA levels at week 24 were achieved in 73.52% of patients (75 out of 102 patients). At week 48, End of treatment response (ETR) rate was 66.67% (68 out of 102 patients). Sustained Virological Response was achieved in 64.7% of patients (66 out of 102 patients).All Hematological side effects were mild to moderate without the need of dose reduction or discontinuation of treatment

A total of **one hundred and forty three (143) chronic hepatitis C naive patients genotype 4** were included in this study. Patients with high degree of liver fibrosis (F4 by Metavir score) and BMI >30 kg/m^2 were excluded. All patients received fixed weekly dose of 160 µg Reiferon Retard® and ribavirin in standard and adjusted doses. Early responders continued treatment for a total of 48 weeks. To confirm the possible impact of menopause on response to treatment we compared sustained virological response (SVR) in all patients below and above 50y age in both genders.The study population included 81 males and 62 females. Overall SVR was (61.5%). SVR was mildly elevated in female patients (66.1%) compared to male patients (58%), but this difference was statistically insignificant (p=0.324). The mean age of responders in female patients was (48.9+3.8y). SVR in male patients <50 y (61.2%) was slightly higher than in male patients >50y (53.1%) but this difference was insignificant (p=0.47). SVR in female patients <50y (76.3%) was significantly higher than in female patients >50y (45.8%), (p=0.0145).

Contraindications:

Peg interferon alfa-2a is contra-indicated in:

- Patients with a history of hypersensitivity to recombinant pegylated interferon alfa-2a or to any of the excipients (See precautions & warnings for use).
- Combination therapy with ribavirin in chronic hepatitis C (also see ribavirin's insert).
- Pregnancy, Nursing mothers & Pediatric use:
  Do not administer Injections preserved with benzyl alcohol to premature infants, neonates, infants below 13 years, pregnant women or nursing mothers. Benzyl alcohol has been associated with serious adverse events & death, particularly in pediatric patients (it may cause Gasping syndrome) Preservative free injections should be used in these populations.
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months
- Initiation of pegylated interferon alfa-2a is contraindicated in HIV-HCV patients with cirrhosis and a Child-Pugh score 6, except if only due to indirect hyperbilirubinaemia caused by drugs such as atazanavir and indinavir
- For contraindications to ribavirin, please refer also to the ribavirin Summary of Product Characteristics (SPC) when pegylated interferon alfa-2a is to be used in combination with ribavirin.

Precautions & Warnings for Use:
Like other pegylated interferons
Psychiatric and central nervous system (CNS)
Like other interferons Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Reiferon Retard® therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behavior (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, like other interferons, it is recommended that treatment with Reiferon Retard® be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions: If treatment with Reiferon Retard® is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualized diagnostic and therapeutic management of the psychiatric condition.

- Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Reiferon Retard® is to be used in combination with ribavirin.
- All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 or 3) treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is required prior to commencing treatment.
- In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV genotype, age, extrahepatic manifestations, risk of transmission, etc, which influence the decision to treat or not.
- Excipient: Benzyl alcohol: Reiferon Retard® is contraindicated in infants or young children up to 13 years of age because of the excipient benzyl alcohol.
- ..., the product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue.

This product is contraindicated for use in premature infants because the formulation contains benzyl alcohol.

Laboratory tests prior to and during therapy:
Like other interferons, prior to beginning Reiferon Retard® therapy, standard haematological and biochemical laboratory tests are recommended for all patients.
The following may be considered as baseline values for initiation of treatment:

- Platelet count 90,000/mm^3
- Absolute neutrophil counts 1500/mm^3
- Adequately controlled thyroid function (TSH and T4).

Haematological tests:
Haematological tests should be repeated after 2 and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy.
In clinical trials, pegylated interferon alpha-2a treatment was associated with decrease in both **total white blood cell (WBC) count and absolute neutrophil count (ANC)**, usually starting within the first 2 weeks of treatment. Progressive decrease after 8 weeks of therapy was infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy, reached normal values by 8 weeks in the majority of patients and returned to baseline in all patients after about 16 weeks.
As with other interferons, Reiferon Retard® treatment has been associated with decrease in **platelet count**, which returned to pre-treatment levels during the post-treatment observation period. In some cases, dose modification may be necessary.
The occurrence of **haemoglobin** <10 g/dl) has been observed in up to 6% of chronic hepatitis C patients in clinical trials receiving the combination treatment of Reiferon Retard® with ribavirin. The frequency depends on the treatment duration and the dose of ribavirin. The risk of developing anaemia is higher in the female population.
As with other interferons, caution should be exercised when administering Reiferon Retard® in combination with other potentially myelosuppressive agents.
Myelosuppression and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a PEG interferon and ribavirin concomitantly with azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon cessation of ribavirin and therapy and concomitant azathioprine, and did not recur upon re-introduction of ribavirin alone.
The use of Reiferon Retard® and ribavirin combination therapy in chronic hepatitis C patients who failed prior treatment has not been adequately studied in patients who discontinued prior therapy for hematological adverse events. Physicians considering treatment in these patients should carefully weigh the risks versus the benefits of re-treatment.
Endocrine system:
Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alpha interferons, including Reiferon Retard®. Prior to initiation of Reiferon Retard® therapy, TSH and T4 levels should be evaluated. Reiferon Retard® treatment may be initiated or continued if TSH levels can be maintained in the normal range by medication. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction. As with other interferons, hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Reiferon Retard®. Patients with these conditions who cannot be adequately controlled by medication should not initiate Reiferon Retard® monotherapy nor Reiferon Retard®/ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled adequately with medication should discontinue Reiferon Retard® monotherapy or Reiferon Retard®/ribavirin therapy.
Cardiovascular system:
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alpha interferon therapies, including Reiferon Retard®. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of Reiferon Retard® therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. In patients with cardiovascular disease, anaemia may necessitate dose reduction or discontinuation of ribavirin.
Liver function:
In patients who develop evidence of hepatic decompensation during treatment, Reiferon Retard® should be discontinued. As with other alpha interferons, increases in ALT levels above baseline have been observed in patients treated with Reiferon Retard®, including patients with a viral response. The increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued.

Hypersensitivity:
Serious, acute hypersensitivity reaction (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If this occurs, therapy must be discontinued and appropriate medical therapy instituted immediately. Transient rashes do not necessitate interruption of treatment.
Autoimmune disease:
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed.
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed.
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) and sepsis have been reported during treatment with alpha interferons including Reiferon Retard®. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.
Ocular changes:
As with other interferons retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction, which may result in loss of vision, have been reported in rare instances with Reiferon Retard®. All patients should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination. Patients with preexisting ophthalmologic disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during Reiferon Retard® therapy. Reiferon Retard® treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.
Pulmonary changes:
As with other alpha interferons, pulmonary symptoms, including dyspnoea, pulmonary infiltrates, pneumonia, and pneumonitis have been reported during therapy with Reiferon Retard®. In case of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.
Skin disorder:
Use of alpha interferons has been associated with exacerbation or provocation of psoriasis and sarcoidosis. Like other interferons, Reiferon Retard® must be used with caution in patients with psoriasis, and in cases of onset or worsening of psoriatic lesions, discontinuation of therapy should be considered.
Transplantation:
The safety and efficacy of Reiferon Retard® and ribavirin treatment have not been established in patients with liver and other organs transplantations. Liver and renal graft rejections have not been reported with Reiferon Retard®, alone or in combination with ribavirin.
Dental and periodontal disorders:
Like other interferons, dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Reiferon Retard® and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and oral mucous membranes during long-term treatment with the combination of Reiferon Retard® and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Interactions:

- Since PEG interferon alfa-2a alter cellular metabolism, the potential to modify the activity of other drugs exists.
- In a small study, PEG Interferon alfa-2a was shown to have an effect on specific microsomal enzyme systems. The clinical relevance of these findings is unknown.
- PEG interferon alfa-2a may affect the oxidative metabolic process; this should be borne in mind when prescribing concomitant therapy with drugs metabolized by this route. However, as yet no specific information is available.
- PEG interferon alfa-2a has been reported to reduce the clearance of theophylline.
- As PEG interferon alfa-2a may affect central nervous system functions, interactions could occur following concurrent administration of centrally-acting drugs. The neurotoxic, hematotoxic or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferon.
- In combination therapy with ribavirin in chronic hepatitis C.

HIV-HCV co-infected patients:

- Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased in vitro when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactataemia/lactic acidosis have been reported with use of ribavirin.
- Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia. Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Pregnancy and lactation:
Do not administer Injections preserved with benzyl alcohol to premature infants, neonates, infants below 13 years, pregnant women or nursing mothers. Benzyl alcohol has been associated with serious adverse events & death, particularly in pediatric patients (it may cause Gasping syndrome) Preservative free injections should be used in these populations.

Use with ribavirin.
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 Reiferon Retard 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.

Effects on the ability to drive and machines usage:

PEG interferon alfa-2a has a minor or moderate influence on the ability to drive and use machines. Patients who develop dizziness, confusion, somnolence or fatigue should be cautioned to avoid driving or operating machinery.

Undesirable effects:

Experience from clinical trials in Chronic hepatitis C:
The frequency and severity of the most commonly reported adverse reactions with Reiferon Retard® are similar to those reported with other interferons alfa-2a. The most frequently reported adverse reactions with Reiferon Retard® 160 µg were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy.
Clinical side effects:
Like other interferons, fever was observed in 50% of cases, fatigue in 32 % of cases, chills in 55% of cases, myalgia in 10% of cases, arthlagia in 10% of cases, musculoskeletal pain in 25% of cases, headache in 10% of cases, nausea in 6% of cases, vomiting in 1% of cases , anorexia was reported in 4% of cases, while dyspepsia in 1% of cases , itching in 2% of cases , cough in 1% of cases, hair loss in 3% of cases, injection site reaction in 8% of cases.
Undesirable Effects Reported with PEG interferon alfa-2a Monotherapy for HBV or HCV or in Combination with Ribavirin for HCV Patients:

Body system	Very Common ≥ 1 /10	Common ≥ 1 /100 to < 1 /10	Uncommon ≥ 1 /1000 to < 1 /100	Rare ≥ 1 /10 ,000 to < 1 /1000	Very rare <1/10,000
Infections and infestations		Upper respiratory infection, bronchitis, sinusitis, herpes simplex, fungal, viral and bacterial infections	Pneumonia, skin infection	Endocarditis, otitis externa	
Neoplasms benign and malignant			Hepatic neoplasm		
Blood and lymphatic system disorders		Thrombocytopenia, anaemia, lymphadenopathy	Pancytopenia		Aplastic anemia
Immune system disorders			Sarcoidosis, thyroiditis	Anaphylaxis, systemic lupus erythematosus rheumatoid arthritis	Idiopathic or thrombotic thrombocytopenic purpura
Endocrine disorders		Hypothyroidism, hyperthyroidism	Diabetes	Diabetic ketoacidosis	
Metabolism and Nutrition Disorders	Anorexia		Dehydration		
Psychiatric disorders	Depression*, anxiety, Insomnia*	Emotional disorders, mood alteration Aggression, nervousness, libido decreased	Suicidal ideation, hallucinations	Suicide, psychotic disorder	
Nervous system disorders	Headache, dizziness*, concentration impaired	Memory impairment, syncope, weakness, migraine, paresthesia, hypoesthesia, paresthesia, tremor, taste disturbance, nightmares, somnolence	Peripheral neuropathy	Coma, convulsions, facial palsy	
Eye disorders		Vision blurred, eye pain, eye inflammation, xerophthalmia	Retinal hemorrhage	Optic neuropathy, Papilloedema, retinal vascular disorder, retinopathy, corneal ulcer	Vision loss ,
Ear and labyrinth disorders		Vertigo, earache	Hearing loss		
Cardiac disorders		Tachycardia, palpitations, oedema peripheral		Myocardial infarction, congestive heart failure, angina, supraventricular tachycardia, arrhythmia, atrial fibrillation, pericarditis, cardiomyopathy	
Vascular disorders		Flushing	Hypertension	Cerebral haemorrhage, vasculitis	
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough	Dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, nasal congestion, rhinitis, sore throat	Wheezing	Interstitial pneumonitis including fatal outcome, pulmonary embolism	
Gastrointestinal disorders	Diarrhoea*, nausea*, abdominal pain*	Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, gloositis, stomatitis, flatulence, dry mouth	Gastrointestinal bleeding	Peptic ulcer, pancreatitis	
Hepato-biliary disorders			Hepatic dysfunction	Hepatic failure, cholangitis, fatty liver	

*These adverse reactions were common (≥ 1/100 to < 1/10) in CHB patients treated with PEG interferon alfa-2a monotherapy.
Hematological Side effects:
• As with other interferons, treatment with Reiferon Retard® was associated with decrease in haematological values (leucopenia, neutropenia, lymphopenia, thrombocytopenia and haemoglobin), which generally improved with dose modification, and returned to pre-treatment levels within 4-8 weeks upon cessation of therapy.
• The occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 6 % of chronic hepatitis C patients in clinical trials on the combined treatment of Reiferon Retard® with ribavirin.
• The rate of neutrophil count (<750/ mm3) has been observed in only 9% of cases.
• The rate of thrombocytopenia (<70000/mm3) has been observed in 12% only.
Laboratory values:
As with other interferons, abnormal laboratory values were observed: ALT increase, bilirubin increase, electrolyte disturbance (hyokalaemia, hypocalcaemia, hypophosphataemia), hyperglycaemia, hypoglycaemia and elevated triglycerides.
Anti-interferon antibodies:
As with other interferons, a higher incidence of neutralizing antibodies was seen in chronic hepatitis C. However in neither disease was this correlated with lack of therapeutic response.
Thyroid function:
As with other interferons associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention, the frequencies observed in patients receiving Reiferon Retard®/ribavirin are similar to those observed with other interferons.
Post marketing Adverse Events:
• Infections and infestations:
Sepsis: frequency unknown.
As with other alpha interferons, sepsis has been reported with Reiferon Retard®.
• Blood and lymphatic system disorders:
Pure red cell aplasia: frequency unknown.
As with other alpha interferons, pure red cell aplasia has been reported with Reiferon Retard®.
• Immune system disorders:
Liver and renal graft rejection: frequency unknown.
Liver and renal graft rejections have been reported with Reiferon Retard®, alone or in combination with ribavirin.
A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada disease (see also section 4.4, Autoimmune disease).
• Psychiatric disorders:
Mania: frequency unknown.
As with other alpha interferons, mania and bipolar disorders have been reported with Reiferon Retard®.
Homicidal ideation: frequency unknown.
• Nervous System Disorders:
Cerebral ischemia: frequency unknown.
Eye Disorders:
Serous retinal detachment: frequency unknown.
As with other alpha interferons, serous retinal detachment has been reported with Reiferon Retard®.
• Vascular disorders:
Peripheral ischaemia: frequency unknown.
As with other alpha interferons, peripheral ischaemia has been reported with Reiferon Retard®
• Gastrointestinal disorders:
Ischaemic colitis: frequency unknown.
As with other alpha interferons, ischaemic colitis has been reported with Reiferon Retard®.
• Musculoskeletal connective tissue and bone disorders:
Rhabdomyolysis: frequency unknown.
Overdosage:
There are no reports of over-dosage but repeated large doses of interferon can be associated with profound lethargy, fatigue, prostration and coma. Such patients should be hospitalized for observation and appropriate supportive treatment given. Patients who experience severe reactions to PEG interferon alfa-2a will usually recover within days after discontinuation of therapy, given appropriate supportive care.

Special precautions for storage:
Store vials at 2°C-8°C. Do not freeze. Keep vial in the outer carton.

Presentation:
Box of 1 vial in 1.2ml of 160 µg pegylated Hansenula-derived recombinant liquid interferon.

MINAPHARM

16 x 56 cm