ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection
Pegasys 180 micrograms solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pegasys 135 micrograms solution for injection
Each vial of 1 ml solution contains 135 micrograms peginterferon alfa-2a*.

Pegasys 180 micrograms solution for injection
Each vial of 1 ml solution contains 180 micrograms peginterferon alfa-2a*.

The strength indicates the quantity of the interferon alfa-2a moiety of peginterferon alfa-2a without consideration of the pegylation.

*The active substance, peginterferon alfa-2a, is a covalent conjugate of the protein interferon alfa-2a produced by recombinant DNA technology in *Escherichia coli* with bis-[monomethoxy polyethylene glycol].

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1.

Excipient with known effect: Benzyl alcohol (10 mg/ 1 ml)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is clear and colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B

Pegasys is indicated for the treatment of hepatitis B envelope antigen (HBeAg)-positive or HBeAg-negative-chronic hepatitis B (CHB) in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis (see sections 4.4 and 5.1).

Chronic hepatitis C

Adult patients

Pegasys is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC) in patients with compensated liver disease (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.2 and 5.1.

Paediatric patients 5 years of age and older:
Pegasys in combination with ribavirin is indicated for the treatment of chronic hepatitis C in treatment-naïve children and adolescents 5 years of age and older who are positive for serum HCV-RNA.

When deciding to initiate treatment in childhood, it is important to consider growth inhibition induced by combination therapy. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

4.2 Posology and method of administration

Treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis B or C.

Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Pegasys.
Monotherapy for hepatitis C should only be considered in cases of contraindication to other medicinal products.

Posology

Chronic hepatitis B – adult patients

The recommended dosage and duration of Pegasys for both HBeAg-positive and HBeAg-negative chronic hepatitis B is 180 micrograms once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

Chronic hepatitis C – treatment-naïve adult patients

The recommended dose for Pegasys is 180 micrograms once weekly by subcutaneous administration in the abdomen or thigh given in combination with oral ribavirin or as monotherapy.

The dose of ribavirin to be used in combination with Pegasys is given in Table 1.
The ribavirin dose should be administered with food.

Duration of treatment – dual therapy with Pegasys and ribavirin

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 regardless of pre-treatment viral load should receive 48 weeks of therapy.
Treatment for 24 weeks may be considered in patients infected with
- genotype 1 with low viral load (LVL) (≤ 800,000 IU/ml) at baseline or
- genotype 4

who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1). In these patients, tolerability to combination therapy and additional prognostic factors such as degree of fibrosis should be taken into account when deciding on treatment duration. Shortening the treatment duration in patients with genotype 1 and high viral load (HVL) (>800, 000 IU/ml) at baseline who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24 should be considered with even more caution since the limited data available suggest that this may significantly negatively impact the sustained virologic response.

Patients infected with HCV genotype 2 or 3 who have detectable HCV RNA at week 4, regardless of pre-treatment viral load should receive 24 weeks of therapy. Treatment for only 16 weeks may be considered in selected patients infected with genotype 2 or 3 with LVL (≤ 800,000 IU/ml) at baseline who become HCV negative by week 4 of treatment and remains HCV negative by week 16. Overall 16 weeks of treatment may be associated with a lower chance of response and is associated with a

higher risk of relapse than a 24 week treatment duration (see section 5.1). In these patients, tolerability to combination therapy and the presence of additional clinical or prognostic factors such as degree of fibrosis should be taken into account when considering deviations from standard 24 weeks treatment duration. Shortening the treatment duration in patients infected with genotype 2 or 3 with HVL (> 800,000 IU/ml) at baseline who become HCV negative by week 4 should be considered with more caution as this may significantly negatively impact the sustained virological response (see Table 1).

Available data for patients infected with genotype 5 or 6 are limited; therefore combination treatment with 1,000/1,200 mg of ribavirin for 48 weeks is recommended.

Table 1: Dosing recommendations for combination therapy for HCV patients

Genotype	Pegasys dose	Ribavirin dose	Duration
Genotype 1 LVL with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 4 with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 2 or 3 without RVR**	180 micrograms	800 mg	24 weeks
Genotype 2 or 3 LVL with RVR**	180 micrograms	800 mg[(a)]	16 weeks[(a)] or 24 weeks
Genotype 2 or 3 HVL with RVR**	180 micrograms	800 mg	24 weeks

*RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24;
**RVR = rapid viral response (HCV RNA negative) by week 4
LVL = ≤ 800,000 IU/ml; HVL = > 800,000 IU/ml
[(a)] It is presently not clear whether a higher dose of ribavirin (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The ultimate clinical impact of a shortened initial treatment of 16 weeks instead of 24 weeks is unknown, taking into account the need for re-treating non-responding and relapsing patients.

The recommended duration of Pegasys monotherapy is 48 weeks.

Chronic hepatitis C – treatment-experienced adult patients

The recommended dose of Pegasys in combination with ribavirin is 180 mcg once weekly by subcutaneous administration. For patients <75 kg and ≥75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, and regardless of genotype, should be administered.
Patients who have detectable virus at week 12 should stop therapy. The recommended total duration of therapy is 48 weeks. If patients infected with virus genotype 1, not responding to prior treatment with peginterferon and ribavirin are considered for treatment, the recommended total duration of therapy is 72 weeks (see section 5.1).

HIV-HCV co-infected adult patients

The recommended dosage for Pegasys, alone or in combination with ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks. For patients infected with HCV genotype 1 <75 kg and ≥75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, should be administered. Patients infected with HCV genotypes other than genotype 1 should receive 800 mg daily of ribavirin. A duration of therapy less than 48 weeks has not been adequately studied.

Duration of therapy when Pegasys is used in combination with other medicinal products
Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Pegasys.

Predictability of response and non-response with Pegasys and ribavirin dual therapy – treatment-naïve patients

Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see Tables 2 and 12).

Table 2: Predictive value of week 12 virological response at the recommended dosing regimen while on Pegasys combination therapy

Genotype	**Negative**			**Positive**		
	No response by week 12	No sustained response	Predictive Value	Response by week 12	Sustained response	Predictive Value
Genotype 1 (N= 569)	102	97	**95%** (97/102)	467	271	**58%** (271/467)
Genotype 2 and 3 (N=96)	3	3	**100%** (3/3)	93	81	**87%** (81/93)

The negative predictive value for sustained response in patients treated with Pegasys in monotherapy was 98%.
A similar negative predictive value has been observed in HIV-HCV co-infected patients treated with Pegasys monotherapy or in combination with ribavirin (100% (130/130) or 98% (83/85), respectively). Positive predictive values of 45% (50/110) and 70% (59/84) were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Predictability of response and non-response with Pegasys and ribavirin dual therapy – treatment-experienced patients

In non-responder patients re-treated for 48 or 72 weeks, viral suppression at week 12 (undetectable HCV RNA defined as <50 IU/ml) has been shown to be predictive for sustained virological response. The probabilities of not achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was not achieved at week 12 were 96% (363 of 380) and 96% (324 of 339), respectively. The probabilities of achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was achieved at week 12 were 35% (20 of 57) and 57% (57 of 100), respectively.

Dose adjustment for adverse reactions in adult patients

General
Where dose adjustment is required for moderate to severe adverse reactions (clinical and/or laboratory) initial dose reduction to 135 micrograms is generally adequate for adult patients. In some cases, dose reduction to 90 micrograms or 45 micrograms is necessary. Dose increases to or towards the original dose may be considered when the adverse reaction abates (see sections 4.4 and 4.8).

Haematological (see also Table 3)
For adults, dose reduction is recommended if the neutrophil count is < 750/mm^3. For patients with Absolute Neutrophil Count (ANC) < 500/mm^3 treatment should be suspended until ANC values return to > 1000/mm^3. Therapy should initially be re-instituted at 90 micrograms Pegasys and the neutrophil count monitored. Guidance for dose reduction based on ANC levels for paediatric patients is provided in Table 7.

Dose reduction to 90 micrograms is recommended if the platelet count is < 50,000/mm^3. Cessation of therapy is recommended when platelet count decreases to levels < 25,000/mm^3.

Specific recommendations for management of treatment-emergent anaemia in adults are as follows: ribavirin should be reduced to 600 milligrams/day (200 milligrams in the morning and 400 milligrams in the evening) if either of the following apply: (1) a patient without significant cardiovascular disease experiences a fall in haemoglobin to < 10 g/dl and ≥ 8.5 g/dl, or (2) a patient with stable cardiovascular disease experiences a fall in haemoglobin by ≥ 2 g/dl during any 4 weeks of treatment. A return to original dosing is not recommended. Ribavirin should be discontinued if either of the following applies: (1) a patient without significant cardiovascular disease experiences a fall in haemoglobin confirmed to < 8.5 g/dl; (2) a patient with stable cardiovascular disease maintains a haemoglobin value < 12 g/dl despite 4 weeks on a reduced dose. If the abnormality is reversed, ribavirin may be restarted at 600 milligrams daily, and further increased to 800 milligrams daily at the discretion of the treating physician. A return to original dosing is not recommended.

Table 3: Dose adjustment for adverse reaction (for further guidance see also text above)

	Reduce ribavirin to 600 mg	Withhold ribavirin	Reduce Pegasys to 135/90/45 micrograms	Withhold Pegasys	Discontinue combination
Absolute Neutrophil Count			< 750/mm^3	< 500/mm^3	
Platelet Count			< 50,000/mm^3 > 25,000/mm^3		< 25,000/mm^3
Haemoglobin - no cardiac disease	< 10 g/dl, and ≥ 8.5 g/dl	< 8.5 g/dl			
Haemoglobin - stable cardiac disease	decrease ≥ 2 g/dl during any 4 weeks	< 12 g/dl despite 4 weeks at reduced dose			

In case of intolerance to ribavirin, Pegasys monotherapy should be continued.

Liver function
Fluctuations in abnormalities of liver function tests are common in patients with chronic hepatitis C. Increases in ALT levels above baseline (BL) have been observed in patients treated with Pegasys, including patients with a virological response.
In chronic hepatitis C clinical trials with adult patients, isolated increases in ALT (≥ 10x ULN, or ≥ 2x BL for patients with a BL ALT ≥ 10x ULN) which resolved without dose-modification were observed in 8 of 451 patients treated with combination therapy. If ALT increase is progressive or persistent, the dose should be reduced initially to 135 micrograms. When increases in ALT levels are progressive despite dose reduction, or are accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see section 4.4). Guidance for dose reduction based on ALT levels for paediatric patients is provided in Table 7.

For chronic hepatitis B patients, transient flares of ALT levels sometimes exceeding 10 times the upper limit of normal are not uncommon, and may reflect immune clearance. Treatment should normally not be initiated if ALT is >10 times the upper limit of normal. Consideration should be given to continuing treatment with more frequent monitoring of liver function during ALT flares. If the Pegasys dose is reduced or withheld, therapy can be restored once the flare is subsiding (see section 4.4).

Special populations

Elderly
Adjustments in the recommended dosage of 180 micrograms once weekly are not necessary when instituting Pegasys therapy in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is required for adult patients with mild or moderate renal impairment. A reduced dose of 135 mcg once weekly is recommended in adult patients with severe renal impairment or end stage renal disease (see section 5.2). Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of Pegasys during the course of therapy should be made in the event of adverse reactions.

Hepatic impairment
In patients with compensated cirrhosis (e.g., Child-Pugh A), Pegasys has been shown to be effective and safe. Pegasys has not been evaluated in patients with decompensated cirrhosis (e.g., Child-Pugh B or C or bleeding oesophageal varices) (see section 4.3).

The Child-Pugh classification divides patients into groups A, B, and C, or "Mild", "Moderate" and "Severe" corresponding to scores of 5-6, 7-9 and 10-15, respectively.

Modified Assessment

Assessment	Degree of abnormality	Score
Encephalopathy	None Grade 1-2 Grade 3-4*	1 2 3
Ascites	Absent Slight Moderate	1 2 3
S-Bilirubin (mg/dl) SI unit = μmol/l)	<2 2.0-3 >3 <34 34-51 >51	1 2 3 1 2 3
S-Albumin (g/dl)	>3.5 3.5-2.8 <2.8	1 2 3
INR	<1.7 1.7-2.3 >2.3	1 2 3

*Grading according to Trey, Burns and Saunders (1966)

Paediatric population

Pegasys is contraindicated in neonates and young children up to 3 years old due to the excipient benzyl alcohol (see sections 4.3 and 4.4).

For children and adolescents aged 5 to 17 years with chronic hepatitis C, and having a Body Surface Area (BSA) greater than 0.7 m^2, the recommended doses for Pegasys and ribavirin are provided in Table 4 and Table 5. It is recommended that Pegasys pre-filled syringes be used for paediatric patients. The Pegasys pre-filled pens do not allow for appropriate adjustment of dosing in these patients. Patients who initiate treatment prior to their 18^{th} birthday should maintain paediatric dosing through the completion of therapy.

Pegasys should not be used in children with a Body Surface Area (BSA) less than 0.71 as there is no available data for this subpopulation.

To calculate BSA, it is recommended to use Mosteller's equation:

$$BSA\ (m^2) = \sqrt{\left(\frac{Height\ (cm) \times Weight\ (kg)}{3600}\right)}$$

Duration of treatment
The duration of treatment with Pegasys in combination with ribavirin in paediatric patients with chronic hepatitis C depends on viral genotype. Patients infected with viral genotypes 2 or 3 should receive 24 weeks of treatment, while patients infected with any other genotype should receive 48 weeks of therapy.

Patients who still have detectable levels of HCV-RNA despite an initial 24 weeks of therapy, should discontinue therapy, as it is unlikely they will be able to achieve a sustained virological response with continued therapy.

Table 4: Pegasys dosing recommendations for paediatric patients aged 5 to 17 years

Body Surface Area (BSA) range (m^2)	Weekly dose (mcg)
0.71-0.74	65
0.75-1.08	90
1.09-1.51	135
>1.51	180

For children and adolescents aged 5 to 17 years with chronic hepatitis C, the recommended dose of ribavirin is based on the patient's body weight, with a target dose of 15 mg/kg/day, divided in two daily doses. For children and adolescents 23 kg or greater, a dosing schedule using 200 mg ribavirin tablets is provided in Table 5. Patients and caregivers must not attempt to break the 200 mg tablets.

Table 5: Ribavirin dosing recommendations for paediatric patients aged 5 to 17 years

Body weight kg (lbs)	Ribavirin daily dose (Approx. 15 mg/kg/day)	Ribavirin number of tablets
23 – 33 (51-73)	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
34 – 46 (75-101)	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
47 – 59 (103-131)	800 mg/day	2 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
60 – 74 (132-163)	1000 mg/day	2 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.
≥75 (>165)	1200 mg/day	3 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.

Dose adjustment for adverse reactions in paediatric patients

For paediatric patients, based on toxicities (see Table 6), up to three levels of dose modification can be made before dose interruption or discontinuation is considered.

Table 6: Pegasys dose modification recommendations in paediatric patients

Starting dose (mcg)	**1 level reduction (mcg)**	**2 level reduction (mcg)**	**3 level reduction (mcg)**
65	45	30	20
90	65	45	20
135	90	65	30
180	135	90	45

If toxicities occur which may be related to Pegasys and/or ribavirin administration, the dose of one or both medicinal products can be reduced. Additionally, ribavirin or Pegasys plus ribavirin combination therapy can be discontinued. It is important to note that ribavirin should never be given as monotherapy. Recommendations for dose modifications for toxicities known to have an association with Pegasys administration that are specific for the paediatric population are presented in Table 7. Unless otherwise noted, the management of all other toxicities should follow the adult recommendations.

Table 7: Pegasys dose modification recommendations for toxicities in paediatric patients

Toxicity	Pegasys dose modification
Neutropenia	750-999 cells/mm^3: Week 1-2 - immediate 1 level adjustment; Week 3-48: no modification. 500-749 cells/mm^3: Week 1-2 - interrupt dosing until >750 cells/mm^3 then resume dose with a 1 level adjustment, assess weekly for the next 3 weeks to verify ANC >750 cells/mm^3; Week 3-48 - immediate 1 level adjustment. 250-499 cells/mm^3: Week 1-2 - interrupt dosing until >750 cells/mm^3 then resume dose with a 2 level adjustment; Week 3-48 - interrupt dosing until >750 cells/mm^3 then resume dose with a 1 level adjustment. < 250 cells/mm^3 (or febrile neutropenia) discontinue treatment.
Increased alanine transaminase (ALT)	For persistent or increasing elevations ≥5 but <10 x ULN, reduce dose with a 1 level adjustment and monitor weekly ALT level to ensure it is stable or decreasing For persistent ALT values ≥10 x ULN discontinue treatment.

In paediatric patients, ribavirin treatment-associated toxicities, such as treatment-emergent anaemia, will be managed by reduction of the full dose. The dose reduction levels are provided in Table 8.

Table 8: Ribavirin dose modification recommendations in paediatric patients

Full dose (Approx. 15 mg/kg/day)	One step dose modification (Approx. 7.5 mg/kg/day)	Ribavirin number of tablets
400 mg/day	200 mg/day	1 x 200 mg tablets A.M.
600 mg/day	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
800 mg/day	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
1000 mg/day	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
1200 mg/day	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.

There is limited experience with Pegasys in treating paediatric patients with HCV aged 3 to 5 years, or who have failed to be adequately treated previously. There are no data in paediatric patients coinfected with HCV/HIV or with renal impairment.

Method of administration

Pegasys is administered subcutaneously in the abdomen or thigh. Exposure to Pegasys was decreased in studies following administration of Pegasys in the arm (see section 5.2).

Pegasys is designed for administration by the patient or carer. Each vial should be used by one person only and is for single use.

Appropriate training is recommended for non-healthcare professionals administering this medicinal product. The “Instructions for the User”, provided in the carton, must be followed carefully by the patient.

4.3 Contraindications

- Hypersensitivity to the active substance, to alfa interferons, or to any of the excipients listed in section 6.1
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4)
- HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6, except if only due to indirect hyperbilirubinemia caused by medicinal products such as atazanavir and indinavir
- Combination with telbivudine (see section 4.5).
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol (see section 4.4 for benzyl alcohol)
- In paediatric patients, the presence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Pegasys therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alfa interferons. All patients should be closely monitored for any signs or symptoms of psychiatric disorders. If symptoms of psychiatric disorders 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, it is recommended that treatment with Pegasys be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions: If treatment with Pegasys is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
The use of Pegasys in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

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 alfa interferon. If treatment with alfa 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.

Growth and development (children and adolescents): During the course of Pegasys plus ribavirin therapy lasting up to 48 weeks in patients aged 5 to 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1).

The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials on a case by case basis (see sections 4.8 and 5.1).

- It is important to consider that the combination therapy induced a growth inhibition during treatment, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

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

Laboratory tests prior to and during therapy

Prior to beginning Pegasys 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 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 (including glucose monitoring).

In clinical trials, Pegasys treatment was associated with decreases in both total white blood cell (WBC) count and absolute neutrophil count (ANC), usually starting within the first 2 weeks of treatment (see section 4.8). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see section 4.2), reached normal values by 8 weeks in the majority of patients and returned to baseline in all patients after about 16 weeks.

Pegasys treatment has been associated with decreases in platelet count, which returned to pre-treatment levels during the post-treatment observation period (see section 4.8). In some cases, dose modification may be necessary (see section 4.2).

The occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 15% of chronic hepatitis C patients in clinical trials on the combined treatment of Pegasys with ribavirin. The frequency depends on the treatment duration and the dose of ribavirin (see section 4.8,). The risk of developing anaemia is higher in the female population.

Caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a peginterferon and ribavirin concomitantly with azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon re-introduction of either treatment alone (see section 4.5).

The use of Pegasys 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 haematological adverse reactions. 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 alfa interferons, including Pegasys. Prior to initiation of Pegasys therapy, TSH and T4 levels should be evaluated. Pegasys treatment may be initiated or continued if TSH levels can be maintained in the normal range by pharmaceutical means. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see section 4.8). Hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Pegasys (see section 4.8). Patients with these conditions who cannot be effectively controlled by medication should not begin Pegasys monotherapy or Pegasys/ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Pegasys or Pegasys/ribavirin therapy.

Cardiovascular system
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alfa interferon therapies, including Pegasys. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of Pegasys 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 (see section 4.2).

Liver function
In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. Increases in ALT levels above baseline have been observed in patients treated with Pegasys, including patients with a viral response. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued (see sections 4.2 and 4.8).

In chronic hepatitis B, unlike chronic hepatitis C, disease exacerbations during therapy are not uncommon and are characterised by transient and potentially significant increases in serum ALT. In clinical trials with Pegasys in HBV, marked transaminase flares have been accompanied by mild changes in other measures of hepatic function and without evidence of hepatic decompensation. In approximately half the cases of flares exceeding 10 times the upper limit of normal, Pegasys dosing was reduced or withheld until the transaminase elevations subsided, while in the rest therapy was continued unchanged. More frequent monitoring of hepatic function was recommended in all instances.

Hypersensitivity
Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alfa 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 alfa 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 re-assessed (see also *Endocrine system* in sections 4.4 and 4.8).

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 (see section 4.8).

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 alfa interferons including Pegasys. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

Ocular changes
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 Pegasys. 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. Adult and paediatric patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during Pegasys therapy. Pegasys treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Pulmonary changes
Pulmonary symptoms, including dyspnoea, pulmonary infiltrates, pneumonia, and pneumonitis have been reported during therapy with Pegasys. In case of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.

Skin disorder
Use of alfa interferons has been associated with exacerbation or provocation of psoriasis and sarcoidosis. Pegasys 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 Pegasys and ribavirin treatment have not been established in patients with liver and other transplantations. Liver and renal graft rejections have been reported with Pegasys, alone or in combination with ribavirin.

HIV-HCV coinfection
Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with Pegasys with or without ribavirin. In study NR15961, patients concurrently treated with stavudine and interferon therapy with or without ribavirin, the incidence of pancreatitis and/or lactic acidosis was 3% (12/398).

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

Co-infected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with ribavirin in combination with interferons, including Pegasys. Baseline variables in co-infected cirrhotic patients that may be associated with hepatic decompensation include: increased serum bilirubin, decreased haemoglobin, increased alkaline phosphatase or decreased platelet count, and treatment with didanosine (ddI).

The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

During treatment, co-infected patients should be closely monitored for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function; e.g., Child-Pugh score of 7 or greater). The Child-Pugh scoring may be affected by factors related to treatment (i.e. indirect hyperbilirubinemia, decreased albumin) and not necessarily

attributable to hepatic decompensation. Treatment with Pegasys should be discontinued immediately in patients with hepatic decompensation.

In patients co-infected with HIV-HCV, limited efficacy and safety data are available in patients with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Pegasys and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Pegasys 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.

Use of peginterferon as long term maintenance monotherapy (unapproved use)
In a randomised, controlled US study (HALT-C) of HCV non-responder patients with varied degrees of fibrosis where 3.5 years of treatment with 90 micrograms/week of Pegasys monotherapy was studied, no significant reductions were observed in the rate of fibrosis progression or related clinical events.

Excipient
Pegasys contains benzyl alcohol. Must not be given to premature babies or neonates. May cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Administration of Pegasys 180 micrograms once weekly for 4 weeks in healthy male subjects did not show any effect on mephenytoin, dapsone, debrisoquine and tolbutamide pharmacokinetics profiles, suggesting that Pegasys has no effect on *in vivo* metabolic activity of cytochrome P450 3A4, 2C9, 2C19 and 2D6 isozymes.

In the same study, a 25% increase in the AUC of theophylline (marker of cytochrome P450 1A2 activity) was observed, demonstrating that Pegasys is an inhibitor of cytochrome P450 1A2 activity. Serum concentrations of theophylline should be monitored and appropriate dose adjustments of theophylline made for patients taking theophylline and Pegasys concomitantly. The interaction between theophylline and Pegasys is likely to be maximal after more than 4 weeks of Pegasys therapy.

HCV monoinfected patients and HBV monoinfected patients

In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95 mg; range 30 mg to 150 mg), treatment with Pegasys 180 micrograms sc once weekly for 4 weeks was associated with mean methadone levels that were 10% to 15% higher than at baseline. The clinical significance of this finding is unknown; nonetheless, patients should be monitored for the signs and symptoms of methadone toxicity. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of peginterferon alfa-2a and ribavirin concomitantly with azathioprin should be avoided. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicinal products should be stopped (see section 4.4).

Results from pharmacokinetic substudies of pivotal phase III trials demonstrated no pharmacokinetic interaction of lamivudine on Pegasys in HBV patients or between Pegasys and ribavirin in HCV patients.

A clinical trial investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration for the treatment of HBV, indicates that the combination is associated with an increased risk for developing peripheral neuropathy. The mechanism behind these events is not known; thus, co-treatment with telbivudine and other interferons (pegylated or standard) may also entail an excess risk. Moreover, the benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established. Therefore, the combination of Pegasys with telbivudine is contraindicated (see section 4.3).

HIV-HCV co-infected patients

No apparent evidence of drug interaction was observed in 47 HIV-HCV co-infected patients who completed a 12 week pharmacokinetic substudy to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine and zidovudine or stavudine). However, due to high variability, the confidence intervals were quite wide. Plasma exposure of ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).

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 (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral therapy regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of peginterferon alfa-2a in pregnant women. Studies in animals with interferon alfa-2a have shown reproductive toxicity (see section 5.3) and the potential risk for humans is unknown. Pegasys is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

It is unknown whether peginterferon alfa-2a/metabolites are excreted in human milk. Because of the potential for adverse reactions in breastfed infants, breastfeeding should be discontinued prior to initiation of treatment.

Fertility

There are no data on the effects of peginterferon alfa-2a on fertility in women. A prolongation of the menstrual cycle has been seen with peginterferon alfa-2a in female monkeys (see section 5.3).

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 Pegasys in combination with ribavirin. Female patients of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded. Please refer to the ribavirin SmPC.

4.7 Effects on ability to drive and use machines

Pegasys has 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.

4.8 Undesirable effects

Summary of the safety profile

Chronic hepatitis C

The frequency and severity of the most commonly reported adverse reactions with Pegasys are similar to those reported with interferon alfa-2a (see Table 9). The most frequently reported adverse reactions with Pegasys 180 micrograms were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy.

Chronic hepatitis B

In clinical trials of 48 weeks treatment and 24 weeks follow-up, the safety profile for Pegasys in chronic hepatitis B was similar to that seen in chronic hepatitis C. With the exception of pyrexia the frequency of the majority of the reported adverse reactions was notably less in CHB patients treated with Pegasys monotherapy compared with HCV patients treated with Pegasys monotherapy (see Table 9) Adverse events were experienced by 88% of Pegasys-treated patients as compared with 53% of patients in the lamivudine comparator group, while 6% of the Pegasys-treated and 4% of the lamivudine-treated patients experienced serious adverse events during the studies. Adverse events or laboratory abnormalities led to 5% of patients withdrawing from Pegasys treatment, while less than 1% of patients withdrew from lamivudine treatment for these reasons. The percentage of patients with cirrhosis who withdrew from treatment was similar to that of the overall population in each treatment group.

Chronic hepatitis C in prior non-responder patients

Overall, the safety profile for Pegasys in combination with ribavirin in prior non-responder patients was similar to that in naïve patients. In a clinical trial of non-responder patients to prior pegylated interferon alfa-2b/ribavirin, which exposed patients to either 48 or 72 weeks of treatment, the frequency of withdrawal for adverse events or laboratory abnormalities from Pegasys treatment and ribavirin treatment was 6% and 7%, respectively, in the 48 week arms and 12% and 13%, respectively, in the 72 week arms. Similarly for patients with cirrhosis or transition to cirrhosis, the frequencies of withdrawal from Pegasys treatment and ribavirin treatment were higher in the 72-week treatment arms (13% and 15%) than in the 48-week arms (6% and 6%). Patients who withdrew from previous therapy with pegylated interferon alfa-2b/ribavirin because of haematological toxicity were excluded from enrolling in this trial.

In another clinical trial, non-responder patients with advanced fibrosis or cirrhosis (Ishak score of 3 to 6) and baseline platelet counts as low as 50,000/mm^3 were treated for 48 weeks. Haematologic laboratory abnormalities observed during the first 20 weeks of the trial included anaemia (26% of patients experienced a haemoglobin level of <10 g/dl), neutropenia (30% experienced an ANC <750/mm^3), and thrombocytopenia (13% experienced a platelet count <50,000/ mm^3) (see section 4.4).

Chronic hepatitis C and HIV co-infection

In HIV-HCV co-infected patients, the clinical adverse reaction profiles reported for Pegasys, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients For HIV-HCV patients receiving Pegasys and ribavirin combination therapy other undesirable effects have been reported in ≥ 1% to ≤ 2% of patients: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia. Pegasys treatment was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of Pegasys had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data are available in co-infected patients with CD4+ cell counts <200/µl.

Tabulated list of adverse reactions

Table 9 summarises the undesirable effects reported with Pegasys monotherapy in CHB or CHC patients and with Pegasys in combination with ribavirin in CHC patients. Undesirable effects reported in clinical studies are grouped according to frequency as follows: 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). For spontaneous reports of undesirable effects from post-marketing experience, the frequency is not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

Table 9: Undesirable effects reported with Pegasys monotherapy for HBV or HCV or in combination with ribavirin for HCV patients in clinical trials and post marketing

Body system	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Infections and infestations		Bronchitis, upper respiratory infection, oral candidiasis, herpes simplex, fungal, viral and bacterial infections	Pneumonia, skin infection	Endocarditis, otitis externa		Sepsis
Neoplasms benign and malignant			Hepatic neoplasm			
Blood and lymphatic system disorders		Thrombocytopenia, anaemia, lymphadenopathy		Pancytopenia	Aplastic anaemia	Pure red cell aplasia
Immune system disorders			Sarcoidosis, thyroiditis	Anaphylaxis, systemic lupus erythematosus, rheumatoid arthritis	Idiopathic or thrombotic thrombocytopenic purpura	Liver and renal graft rejection, Vogt-Koyanagi-Harada disease
Endocrine disorders		Hypothyroidism, hyperthyroidism	Diabetes	Diabetic ketoacidosis		
Metabolism and nutrition disorders	Anorexia		Dehydration			

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Psychiatric disorders	Depression*, anxiety, insomnia*	Aggression, mood alteration, emotional disorders, nervousness, libido decreased	Suicidal ideation, hallucinations	Suicide, psychotic disorder		Mania, bipolar disorders, homicidal ideation
Nervous system disorders	Headache, dizziness*, concentration impaired	Syncope, migraine, memory impairment, weakness, hypoaesthesia, hyperaesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence	Peripheral neuropathy	Coma, convulsions, facial palsy		Cerebral ischaemia
Eye disorders		Vision blurred, eye pain, eye inflammation, xerophthalmia	Retinal haemorrhage	Optic neuropathy, papilloedema, retinal vascular disorder, retinopathy, corneal ulcer	Vision loss	Serous retinal detachment
Ear and labyrinth disorders		Vertigo, earache	Hearing loss			
Cardiac disorders		Tachycardia, oedema peripheral, palpitations,		Myocardial infarction, congestive heart failure, cardiomyopathy, angina, arrhythmia, atrial fibrillation, pericarditis, supraventricular tachycardia		
Vascular disorders		Flushing	Hypertension	Cerebral haemorrhage, vasculitis		Peripheral ischaemia
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		Pulmonary arterial hypertension[§]

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Gastrointestinal disorders	Diarrhoea*, nausea*, abdominal pain*	Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, dry mouth	Gastrointestinal bleeding	Peptic ulcer, pancreatitis		Ischaemic colitis, tongue pigmentation
Hepato-biliary disorders			Hepatic dysfunction	Hepatic failure, cholangitis, fatty liver		
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, pruritis, dry skin	Psoriasis, urticaria, eczema, rash, sweating increased, skin disorder, photosensitivity reaction, night sweats			Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, erythema multiforme	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps		Myositis		Rhabdomyolysis
Renal and urinary disorders				Renal insufficiency		
Reproductive system and breast disorders		Impotence				
General disorders and administration site conditions	Pyrexia, rigors*, pain*, asthenia, fatigue, injection site reaction*, irritability*	Chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst				
Investigations		Weight decreased				
Injury, poisoning and procedural complications				Substance overdose		

*These adverse reactions were common (**≥1/100 to < 1/10)** in CHB patients treated with Pegasys monotherapy

§ Class label for interferon products, see below Pulmonary arterial hypertension.

Description of selected adverse reactions

Pulmonary arterial hypertension
Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

Laboratory values
Pegasys treatment was associated with abnormal laboratory values: ALT increase, bilirubin increase, electrolyte disturbance (hypokalaemia, hypocalcaemia, hypophosphataemia), hyperglycaemia, hypoglycaemia and elevated triglycerides (see section 4.4.). With both Pegasys monotherapy, and also the combined treatment with ribavirin, up to 2% of patients experienced increased ALT levels that led to dose modification or discontinuation of the treatment.

Treatment with Pegasys was associated with decreases 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 (see sections 4.2 and 4.4).

Moderate (ANC: 0.749 - 0.5 x 10^9/l) and severe (ANC: < 0.5 x 10^9/l) neutropenia was observed respectively in 24% (216/887) and 5% (41/887) of patients receiving Pegasys 180 micrograms and ribavirin 1000/1200 milligrams for 48 weeks.

Anti-interferon antibodies
1-5% of patients treated with Pegasys developed neutralising anti-interferon antibodies. As with other interferons, a higher incidence of neutralising antibodies was seen in chronic hepatitis B. However in neither disease was this correlated with lack of therapeutic response.

Thyroid function
Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see section 4.4). The frequencies observed (4.9%) in patients receiving Pegasys/ribavirin (NV15801) are similar to those observed with other interferons.

Laboratory values for HIV-HCV co-infected patients
Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment. Decrease in ANC levels below 500 cells/mm^3 was observed in 13% and 11% of patients receiving Pegasys monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm^3 was observed in 10% and 8% of patients receiving Pegasys monotherapy and combination therapy, respectively. Anaemia (haemoglobin < 10 g/dl) was reported in 7% and 14% of patients treated with Pegasys monotherapy or in combination therapy, respectively.

Paediatric population

Chronic hepatitis C

In a clinical trial with 114 paediatric patients (5 to 17 years of age) treated with Pegasys alone or in combination with ribavirin (see section 5.1), dose modifications were required in approximately one-third of patients, most commonly for neutropenia and anaemia. In general, the safety profile observed in paediatric patients was similar to that seen in adults. In the paediatric study, the most prevalent adverse reactions in patients treated with combination therapy for up to 48 weeks with Pegasys and ribavirin were influenza-like illness (91%), headache (64%), gastrointestinal disorder (56%), and injection-site reaction (45%). A full listing of adverse reactions reported in this treatment group (n=55) is provided in Table 10. Seven patients receiving combination Pegasys and ribavirin treatment for 48 weeks discontinued therapy for safety reasons (depression, psychiatric evaluation abnormal, transient

blindness, retinal exudates, hyperglycaemia, type 1 diabetes mellitus, and anaemia). Most of the adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 2 patients in the Pegasys plus ribavirin combination therapy group (hyperglycaemia and cholecystectomy).

Table 10: Adverse reactions reported among paediatric patients infected with HCV and assigned to Pegasys plus ribavirin in study NV17424

Body system	Very common	Common
Infections and infestations		Infectious mononucleosis, pharyngitis streptococcal, influenza, gastroenteritis viral, candidiasis, gastroenteritis, tooth abscess, hordeolum, urinary tract infection, , nasopharyngitis
Blood and lymphatic system disorders		Anaemia
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia, type 1 diabetes mellitus
Psychiatric disorders	Insomnia	Depression, anxiety, hallucination, abnormal behaviour, aggression, anger, attention deficit / hyperactivity disorder
Nervous system disorders	Headache	Dizziness, disturbance in attention, migraine
Eye disorders		Blindness transient, retinal exudates, visual impairment, eye irritation, eye pain, eye pruritis
Ear and labyrinth disorders		Ear pain
Respiratory, thoracic and mediastinal disorders		Dyspnoea, epistaxis
Gastrointestinal disorders	Gastrointestinal disorder	Abdominal pain upper, stomatitis, nausea, aphthous stomatitis, oral disorder
Skin and subcutaneous tissue disorders	Rash, pruritus, alopecia	Swollen face, drug eruption
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Back pain, pain in extremity
Renal and urinary disorders		Dysuria, incontinence, urinary tract disorder
Reproductive system and breast disorders		Vaginal discharge
General disorders and administration site conditions	Influenza-like illness, injection site reaction, irritability, fatigue	Pyrexia, vessel puncture site haematoma, pain
Investigations		Psychiatric evaluation abnormal
Surgical and medical procedures		Tooth extraction, cholecystectomy
Social circumstances		Educational problem

Growth inhibition was observed in paediatric patients (see section 4.4). Paediatric patients treated with Pegasys plus ribavirin combination therapy showed a delay in weight and height increases after 48 weeks of therapy compared with baseline. Patient ‘weight for age’ and ‘height for age’ percentiles of the normative population decreased during treatment. At the end of 2 years follow-up after treatment, most patients had returned to baseline normative growth curve percentiles for weight and height (mean weight percentile was 64% at baseline and 60% at 2 years post-treatment; mean height percentile was 54% at baseline and 56% at 2 years post-treatment). At the end of treatment, 43% of patients experienced a weight percentile decrease of 15 percentiles or more, and 25% (13 of 53) experienced a height percentile decrease of 15 percentiles or more on the normative growth curves. At 2 years post-treatment, 16% (6 of 38) of patients remained 15 percentiles or more below their baseline weight curve and 11% (4 of 38) remained 15 percentiles or more below their baseline height curve.

55% (21 of 38) of subjects who completed the original study enrolled in the long-term follow up extending up to 6 years post-treatment. The study demonstrated that the post-treatment recovery in growth at 2 years post-treatment was maintained to 6 years post-treatment. For a few subjects who were more than 15 percentiles below their baseline height curve at 2 years post-treatment, they either returned to baseline comparable height percentiles at 6 years post-treatment or a non-treatment related causative factor has been identified. The extent of available data is not sufficient to conclude that growth inhibition due to Pegasys exposure is always reversible.

Laboratory values
Decreases in haemoglobin, neutrophils and platelets may require dose reduction or permanent discontinuation from treatment (see Table 3 and Table 7). Most laboratory abnormalities noted during the clinical trial returned to baseline levels shortly after discontinuation of treatment.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

Overdoses involving between two injections on consecutive days (instead of weekly interval) up to daily injections for 1 week (i.e., 1260 micrograms/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 micrograms have been administered in renal cell carcinoma and chronic myelogenous leukaemia clinical trials, respectively. Dose limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia, consistent with interferon therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB11

Mechanism of action

The conjugation of PEG reagent (bis-monomethoxypolyethylene glycol) to interferon alfa-2a forms a pegylated interferon alfa-2a (Pegasys). Pegasys possesses the *in vitro* antiviral and antiproliferative activities that are characteristic of interferon alfa-2a.

Interferon alfa-2a is conjugated with bis-[monomethoxy polyethylene glycol] at a degree of substitution of one mole of polymer/mole of protein. The average molecular mass is approximately 60,000 of which the protein moiety constitutes approximately 20,000.

Pharmacodynamic effects

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received treatment with 180 micrograms Pegasys. The first phase of decline occurs 24 to 36 hours after the first dose of Pegasys and is followed by the second phase of decline which continues over the next 4 to 16 weeks in patients who achieve a sustained response. Ribavirin had no significant effect on the initial viral kinetics over the first 4 to 6 weeks in patients treated with the combination of ribavirin and pegylated interferon alfa-2a or interferon alfa.

Clinical efficacy and safety

Chronic hepatitis B

All clinical trials recruited patients with chronic hepatitis B who had active viral replication measured by HBV DNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. Study WV16240 recruited patients who were positive for HBeAg, while study WV16241 recruited patients who were negative for HBeAg and positive for anti-HBe. In both studies the treatment duration was 48 weeks, with 24 weeks of treatment-free follow-up. Both studies compared Pegasys plus placebo vs Pegasys plus lamivudine vs lamivudine alone. No HBV-HIV co-infected patients were included in these clinical trials.

Response rates at the end of follow-up for the two studies are presented in Table 11. In study WV16240, the primary efficacy endpoints were HBeAg seroconversion and HBV-DNA below 10^5 copies/ml. In study WV16241, the primary efficacy endpoints were ALT normalisation and HBV-DNA below 2×10^4 copies/ml. HBV-DNA was measured by the COBAS AMPLICOR™ HBV MONITOR Assay (limit of detection 200 copies/ml).

A total of 283/1351 (21%) of patients had advanced fibrosis or cirrhosis, 85/1351 (6%) had cirrhosis. There was no difference in response rate between these patients and those without advanced fibrosis or cirrhosis.

Table 11: Serological, virological and biochemical responses in chronic hepatitis B

	HBeAg positive Study WV16240			**HBeAg negative / anti-HBe positive Study WV16241**		
Response Parameter	**Pegasys** 180 mcg & **Placebo** (N=271)	**Pegasys** 180 mcg & **Lamivudine** 100 mg (N=271)	**Lamivudine** 100 mg (N=272)	**Pegasys** 180 mcg & **Placebo** (N=177)	**Pegasys** 180 mcg & **Lamivudine** 100 mg (N=179)	**Lamivudine** 100 mg (N=181)
HBeAg Sero-conversion	32% #	27%	19%	N/A	N/A	N/A
HBV DNA response *	32% #	34%	22%	43% #	44%	29%
ALT Normal-isation	41% #	39%	28%	59% #	60%	44%
HBsAg Sero-conversion	3% #	3%	0%	3%	2%	0%

* For HBeAg-positive patients: HBV DNA < 10^5 copies/ml
For HBeAg-negative/anti-HBe-positive patients: HBV DNA < 2×10^4 copies/ml

p-value (vs. lamivudine) $\leq$ 0.01 (stratified Cochran-Mantel-Haenszel test)

Histological response was similar across the three treatment groups in each study; however, patients showing a sustained response 24 weeks after the end of treatment were significantly more likely to also show histological improvement.

All patients who completed the phase III studies were eligible for entry into a long-term follow-up study (WV16866). Among patients from study WV16240, who received Pegasys monotherapy and entered the long-term follow-up study, the rate of sustained HBeAg seroconversion 12 months after the end of therapy was 48% (73/153). In patients receiving Pegasys monotherapy in study WV16241, the rate of HBV DNA response and ALT normalisation 12 months after end of treatment were 42% (41/97) and 59% (58/99), respectively.

Chronic hepatitis C

Predictability of response
Please refer to section 4.2, in Table 2.

Dose-response in monotherapy
In a direct comparison with 90 micrograms, the 180 micrograms-dose was associated with superior sustained virological response in patients with cirrhosis, but in a study in non-cirrhotic patients very similar results were obtained with doses of 135 micrograms and 180 micrograms.

Confirmatory clinical trials in adult treatment-naïve patients
All clinical trials recruited interferon-naïve patients with chronic hepatitis C confirmed by detectable levels of serum HCV RNA, elevated levels of ALT (with the exception of study NR16071) and a liver biopsy consistent with chronic hepatitis. Study NV15495 specifically recruited patients with a histological diagnosis of cirrhosis (about 80%) or transition to cirrhosis (about 20%). Only HIV-HCV co-infected patients were included in the study NR15961 (see Table 20). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl.
For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see Tables 12, 13, 14 and Table 20, respectively. Virological response was defined as undetectable HCV RNA as measured by the COBAS AMPLICOR™ HCV Test, version 2.0 (limit of detection 100 copies/ml equivalent to 50 International Units/ml) and sustained response as one negative sample approximately 6 months after end of therapy.

Table 12: Virological response in HCV patients

	Pegasys monotherapy				**Pegasys combination therapy**		
	non-cirrhotic and cirrhotic		**cirrhotic**		**non-cirrhotic and cirrhotic**		
	Study NV15496 + NV15497 + NV15801		**Study NV15495**		**Study NV15942**	**Study NV15801**	
	Pegasys 180 mcg (N=701) 48 weeks	**Interferon alfa-2a** 6 MIU/3 MIU & 3 MIU (N=478) 48 weeks	**Pegasys** 180 mcg (N=87) 48 weeks	**Interferon alfa-2a** 3 MIU (N=88) 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg (N=436) 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg (N=453) 48 weeks	**Interferon alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg (N=444) 48 weeks
Response at End of Treatment	55 - 69%	22 - 28%	44%	14%	68%	69%	52%
Overall Sustained Response	28 - 39%	11 - 19%	30%*	8%*	63%	54%**	45%**

* 95% CI for difference: 11% to 33% p-value (stratified Cochran-Mantel-Haenszel test) = 0.001
** 95% CI for difference: 3% to 16% p-value (stratified Cochran-Mantel-Haenszel test) = 0.003

The virological responses of HCV monoinfected patients treated with Pegasys and ribavirin combination therapy in relation to genotype and pre-treatment viral load and in relation to genotype, pre-treatment viral load and rapid virological response at week 4 are summarised in Table 13 and Table 14, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype, baseline viral load and virological response at week 4 (see Tables 1, 13 and 14).
The difference between treatment regimens was in general not influenced by presence/absence of cirrhosis; therefore treatment recommendations for genotype 1, 2 or 3 are independent of this baseline characteristic.

Table 13: Sustained virological response based on genotype and pre-treatment viral load after Pegasys combination therapy with ribavirin in HCV patients

	Study NV15942				Study NV15801	
	Pegasys 180 mcg & **Ribavirin** 800 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Interferon alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg 48 weeks
Genotype 1 Low viral load High viral load	29% (29/101) 41% (21/51) 16% (8/50)	42% (49/118)* 52% (37/71) 26% (12/47)	41% (102/250)* 55% (33/60) 36% (69/190)	52% (142/271)* 65% (55/85) 47% (87/186)	45% (134/298) 53% (61/115) 40% (73/182)	36% (103/285) 44% (41/94) 33% (62/189)
Genotype 2/3 Low viral load High viral load	84% (81/96) 85% (29/34) 84% (52/62)	81% (117/144) 83% (39/47) 80% (78/97)	79% (78/99) 88% (29/33) 74% (49/66)	80% (123/153) 77% (37/48) 82% (86/105)	71% (100/140) 76% (28/37) 70% (72/103)	61% (88/145) 65% (34/52) 58% (54/93)
Genotype 4	(0/5)	(8/12)	(5/8)	(9/11)	(10/13)	(5/11)

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
* Pegasys 180 mcg & ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg & ribavirin 800 mg, 48 w:
Odds Ratio (95% CI) = 1.52 (1.07 to 2.17) P-value (stratified Cochran-Mantel-Haenszel test) = 0.020
* Pegasys 180 mcg & ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg & ribavirin 1000/1200 mg, 24 w:
Odds Ratio (95% CI) = 2.12 (1.30 to 3.46) P-value (stratified Cochran-Mantel-Haenszel test) = 0.002.

The possibility to consider shortening treatment duration to 24 weeks in genotype 1 and 4 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response at week 4 in studies NV15942 and ML17131 (see Table 14).

Table 14: Sustained virological response based on rapid viral response at week 4 for genotype 1 and 4 after Pegasys combination therapy with ribavirin in HCV patients

	Study NV15942		Study ML17131
	Pegasys 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks
Genotype 1 RVR Low viral load High viral load	90% (28/31) 93% (25/27) 75% (3/4)	92% (47/51) 96% (26/27) 88% (21/24)	77% (59/77) 80% (52/65) 58% (7/12)
Genotype 1 non RVR Low viral load High viral load	24% (21/87) 27% (12/44) 21% (9/43)	43% (95/220) 50% (31/62) 41% (64/158)	- - -
Genotype 4 RVR	(5/6)	(5/5)	92% (22/24)
Genotype 4 non RVR	(3/6)	(4/6)	-

Low viral load = ≤ 800,000 IU/ml; High viral load= > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24

Although limited, data indicated that shortening treatment to 24 weeks might be associated with a higher risk of relapse (see Table 15).

Table 15: Relapse of virological response at the end of treatment for rapid virological response population

	Study NV15942		Study NV15801
	Pegasys 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks
Genotype 1 RVR	6.7% (2/30)	4.3% (2/47)	0% (0/24)
Low viral load	3.8% (1/26)	0% (0/25)	0% (0/17)
High viral load	25% (1/4)	9.1% (2/22)	0% (0/7)
Genotype 4 RVR	(0/5)	(0/5)	0% (0/4)

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on a sustained virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 16).

In study NV17317 in patients infected with viral genotype 2 or 3, all patients received Pegasys 180 mcg sc qw and a ribavirin dose of 800 mg and were randomised to treatment for either 16 or 24 weeks. Overall treatment for 16 weeks resulted in lower sustained viral response (65%) than treatment for 24 weeks (76%) ($p < 0.0001$).

The sustained viral response achieved with 16 weeks of treatment and with 24 weeks of treatment was also examined in a retrospective subgroup analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline (see Table 16).

Table 16: Sustained virological response overall and based on rapid viral response by week 4 for genotype 2 or 3 after Pegasys combination therapy with ribavirin in HCV patients

Study NV17317				
	Pegasys 180 mcg & **Ribavirin** 800 mg 16 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	Treatment difference [95%CI]	p value
Genotype 2 or 3	65% (443/679)	76% (478/630)	-10.6% [-15.5% ; -0.06%]	P<0.0001
Genotype 2 or 3 RVR	82% (378/461)	90% (370/410)	-8.2% [-12.8% ; -3.7%]	P=0.0006
Low viral load	89% (147/166)	94% (141/150)	-5.4% [-12% ; 0.9%]	P=0.11
High viral load	78% (231/295)	88% (229/260)	-9.7% [-15.9% ;-3.6%]	P=0.002

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4

It is presently not clear whether a higher dose of ribavirin (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.
The data indicated that shortening treatment to 16 weeks is associated with a higher risk of relapse (see Table 17).

Table 17: Relapse of virological response after the end of treatment in genotype 2 or 3 patients with a rapid viral response

Study NV17317				
	Pegasys 180 mcg & **Ribavirin** 800 mg 16 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	Treatment difference [95%CI]	p value
Genotype 2 or 3 RVR	15% (67/439)	6% (23/386)	9.3% [5.2% ; 13.6%]	P<0.0001
Low viral load	6% (10/155)	1% (2/141)	5% [0.6% ; 10.3%]	P=0.04
High viral load	20% (57/284)	9% (21/245)	11.5% [5.6% ; 17.4%]	P=0.0002

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4

Superior efficacy of Pegasys compared to interferon alfa-2a was demonstrated also in terms of histological response, including patients with cirrhosis and/or HIV-HCV co-infection.

Adult chronic hepatitis C prior treatment non-responder patients
In study MV17150, patients who were non-responders to previous therapy with pegylated interferon alfa-2b plus ribavirin were randomised to four different treatments:

- Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 60 weeks
- Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 36 weeks
- Pegasys 180 mcg/week for 72 weeks
- Pegasys 180 mcg/week for 48 weeks

All patients received ribavirin (1000 or 1200 mg/day) in combination with Pegasys. All treatment arms had 24 week treatment-free follow-up.

Multiple regression and pooled group analyses evaluating the influence of treatment duration and use of induction dosing clearly identified treatment duration for 72 weeks as the primary driver for achieving a sustained virological response. Differences in sustained virological response (SVR) based on treatment duration, demographics and best responses to previous treatment are displayed in Table 18.

Table 18: Week 12 virological response (VR) and sustained virological response (SVR) in patients with virological response at week 12 after treatment with Pegasys and ribavirin combination therapy in nonresponders to peginterferon alfa-2b plus ribavirin

Study MV17150			
	Pegasys 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 72 or 48 Weeks (N = 942) **Pts with VR at Wk 12** [a] **(N = 876)**	**Pegasys** 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 72 Weeks (N = 473) **SVR in Pts with VR at Wk 12** [b] **(N = 100)**	**Pegasys** 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 48 Weeks (N = 469) **SVR in Pts with VR at Wk 12** [b] **(N = 57)**
Overall	18% (157/876)	57% (57/100)	35% (20/57)
Low viral load	35% (56/159)	63% (22/35)	38% (8/21)
High viral load	14% (97/686)	54% (34/63)	32% (11/34)
Genotype 1/4	17% (140/846)	55% (52/94)	35% (16/46)
Low viral load	35% (54/154)	63% (22/35)	37% (7/19)
High viral load	13% (84/663)	52% (30/58)	35% (9/26)
Genotype 2/3	58% (15/26)	(4/5)	(3/10)
Low viral load	(2/5)	—	(1/2)
High viral load	(11/19)	(3/4)	(1/7)
Cirrhosis Status			
Cirrhosis	8% (19/239)	(6/13)	(3/6)
Noncirrhosis	22% (137/633)	59% (51/87)	34% (17/50)
Best Response during Previous Treatment			
$\geq 2\log_{10}$ decline in HCV RNA	28% (34/121)	68% (15/22)	(6/12)
$<2\log_{10}$ decline in HCV RNA	12% (39/323)	64% (16/25)	(5/14)
Missing best previous response	19% (84/432)	49% (26/53)	29% (9/31)

High viral load = > 800,000 IU/ml, low viral load = ≤ 800,000 IU/ml.

[a] Patients who achieved viral suppression (undetectable HCV RNA, < 50 IU/ml) at week 12 were considered to have a virological response at week 12. Patients missing HCV RNA results at week 12 have been excluded from the analysis.

[b] Patients who achieved viral suppression at week 12 but were missing HCV RNA results at the end of follow-up were considered to be non-responders.

In the HALT-C study, patients with chronic hepatitis C and advanced fibrosis or cirrhosis who were non-responders to previous treatment with interferon alfa or pegylated interferon alfa monotherapy or in combination therapy with ribavirin were treated with Pegasys 180 mcg/week and ribavirin 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on Pegasys plus ribavirin combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. The probability for sustained virological response varied depending upon the previous treatment regimen; see Table 19.

Table 19: Sustained virological response in HALT-C by previous treatment regimen in non-responder population

Previous Treatment	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks
Interferon	27% (70/255)
Pegylated interferon	34% (13/38)
Interferon plus ribavirin	13% (90/692)
Pegylated interferon plus ribavirin	11% (7/61)

HIV-HCV co-infected patients
The virological responses of patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and pre-treatment viral load for HIV-HCV co-infected patients are summarised below in Table 20.

Table 20: Sustained virological response based on genotype and pre-treatment viral load after Pegasys combination therapy with ribavirin in HIV-HCV co-infected patients

Study NR15961			
	Interferon alfa-2a 3 MIU & **Ribavirin 800 mg** 48 weeks	**Pegasys** 180 mcg & **Placebo** 48 weeks	**Pegasys** 180 mcg & **Ribavirin 800 mg** 48 weeks
All patients	12% (33/285)*	20% (58/286)*	40% (116/289)*
Genotype 1 Low viral load High viral load	7% (12/171) 19% (8/42) 3% (4/129)	14% (24/175) 38% (17/45) 5% (7/130)	29% (51/176) 61% (28/46) 18% (23/130)
Genotype 2-3 Low viral load High viral load	20% (18/89) 27% (8/30) 17% (10/59)	36% (32/90) 38% (9/24) 35% (23/66)	62% (59/95) 61% (17/28) 63% (42/67)

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
* Pegasys 180 mcg & ribavirin 800 mg vs. Interferon alfa-2a 3 MIU & ribavirin 800 mg:
Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001
* Pegasys 180 mcg & ribavirin 800 mg vs. Pegasys 180 mcg:
Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001
* Interferon alfa-2a 3 MIU & ribavirin 800 mg vs. Pegasys 180 mcg:
Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared treatment using Pegasys 180 mcg/week and either ribavirin 800 mg or 1000 mg (<75 kg)/1200 mg (≥75 kg) daily for 48 weeks. The study was not powered for efficacy considerations. The safety profiles in both ribavirin groups were consistent with the known safety profile of Pegasys plus ribavirin combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose ribavirin arm.

HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomised to receive Pegasys 180 micrograms/week and ribavirin 800 milligrams/day for either 24 or 48 weeks followed by a 24 week treatment free follow-up period or no treatment for 72 weeks. The SVRs reported in the treatment arms of this study were similar to the corresponding treatment arms from study NV15942.

Paediatric population
In the investigator sponsored CHIPS study (Chronic Hepatitis C International Paediatric Study), 65 children and adolescents (6-18 years) with chronic HCV infection were treated with Pegasys 100 mcg/m^2 sc once weekly and ribavirin 15 mg/kg/day for 24 weeks (genotypes 2 and 3) or 48 weeks (all other genotypes). Preliminary and limited safety data demonstrated no obvious departure from the known safety profile of the combination in adults with chronic HCV infection, but, importantly, the potential impact on growth has not been reported. Efficacy results were similar to those reported in adults.

In the NV17424 (PEDS-C) study, previously untreated paediatric patients 5 to 17 years of age (55% <12 years old) with compensated chronic hepatitis C and detectable HCV RNA were treated with Pegasys 180 mcg x BSA/1.73 m^2 once weekly for 48 weeks with or without ribavirin 15 mg/kg/day. All patients were followed for 24 weeks post-treatment. A total of 55 patients received initial combination treatment of Pegasys plus ribavirin, of whom 51% were female, 82% were Caucasian, and 82% were infected with HCV genotype 1. The study efficacy results for these patients are summarised in Table 21.

Table 21: Sustained virological response in the NV17424 study

	Pegasys 180 mcg x BSA/1.73 m² + Ribavirin 15 mg/kg (N=55)*
All HCV genotypes**	29 (53%)
HCV genotype 1	21/45 (47%)
HCV genotype 2 and 3	8/10 (80%)

*Results indicate undetectable HCV-RNA defined as HCV RNA less than 50 IU/ml at 24 weeks post-treatment using the AMPLICOR HCV test v2.
**Scheduled treatment duration was 48 weeks regardless of the genotype

5.2 Pharmacokinetic properties

Absorption
Following a single subcutaneous injection of Pegasys 180 micrograms in healthy subjects, serum concentrations of peginterferon alfa-2a are measurable within 3 to 6 hours. Within 24 hours, about 80% of the peak serum concentration is reached. The absorption of Pegasys is sustained with peak serum concentrations reached 72 to 96 hours after dosing. The absolute bioavailability of Pegasys is 84% and is similar to that seen with interferon alfa-2a.

Distribution
Peginterferon alfa-2a is found predominantly in the bloodstream and extracellular fluid as seen by the volume of distribution at steady-state (V_d) of 6 to 14 litres in humans after intravenous administration. From mass balance, tissue distribution and whole body autoradioluminography studies performed in rats, peginterferon alfa-2a is distributed to the liver, kidney and bone marrow in addition to being highly concentrated in the blood.

Biotransformation
The metabolism of Pegasys is not fully characterised; however studies in rats indicate that the kidney is a major organ for excretion of radiolabelled material.

Elimination
In humans, the systemic clearance of peginterferon alfa-2a is about 100-fold lower than that of the native interferon alfa-2a. After intravenous administration, the terminal half-life of peginterferon alfa-2a in healthy subjects is approximately 60 to 80 hours compared to values of 3-4 hours for standard interferon. The terminal half-life after subcutaneous administration in patients is longer with a mean value of 160 hours (84 to 353 hours). The terminal half-life may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

Linearity/non-linearity
Dose-proportional increases in exposure of Pegasys are seen in healthy subjects and in patients with chronic hepatitis B or C after once-weekly dosing.

In chronic hepatitis B or C patients, peginterferon alfa-2a serum concentrations accumulate 2 to 3 fold after 6 to 8 weeks of once weekly dosing compared to single dose values. There is no further accumulation after 8 weeks of once weekly dosing. The peak to trough ratio after 48 weeks of treatment is about 1.5 to 2. Peginterferon alfa-2a serum concentrations are sustained throughout one full week (168 hours).

Patients with renal impairment
A clinical trial evaluated 50 CHC patients with either moderate (creatinine clearance 30 to 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment, or with end stage renal disease (ESRD) requiring chronic hemodialysis (HD). Patients with moderate renal impairment receiving

Pegasys 180 mcg once weekly exhibited similar peginterferon alfa-2a plasma exposures compared to patients with normal renal function. Patients with severe renal impairment receiving Pegasys 180 mcg once weekly showed a 60% higher peginterferon alfa-2a exposure than patients with normal renal function, therefore a reduced dose of Pegasys 135 mcg once weekly is recommended in patients with severe renal impairment. In 13 patients with ESRD requiring chronic HD, administration of Pegasys 135 mcg once weekly resulted in 34% lower peginterferon alfa-2a exposure than in patients with normal renal function. However, several independent studies have demonstrated the 135mcg dose to be safe, efficacious and well tolerated, in patients with ESRD. (see section 4.2).

Gender
The pharmacokinetics of Pegasys after single subcutaneous injections was comparable between male and female healthy subjects.

Paediatric population
In a population pharmacokinetic study (NR16141), 14 children 2 to 8 years of age with CHC received Pegasys monotherapy at a dose of: 180 mcg x BSA of the child/1.73 m^2. The PK model developed from this study shows a linear influence of BSA on the apparent clearance of the drug over the age range studied. Thus, the lower the BSA of the child, the lower the clearance of the drug and the higher the resultant exposure. The mean exposure (AUC) during the dosing interval is predicted to be 25% to 70% higher than that observed in adults receiving 180 mcg fixed dosing.

Elderly
In subjects older than 62 years, the absorption of Pegasys after a single subcutaneous injection of 180 micrograms was delayed but still sustained compared to young healthy subjects (t_{max} of 115 hours vs. 82 hours, older than 62 years vs. younger, respectively). The AUC was slightly increased (1663 vs. 1295 ng·h/ml) but peak concentrations (9.1 vs. 10.3 ng/ml) were similar in subjects older than 62 years. Based on drug exposure, pharmacodynamic response and tolerability, a lower dose of Pegasys is not needed in the geriatric patient (see section 4.2).

Hepatic impairment
The pharmacokinetics of Pegasys were similar between healthy subjects and patients with hepatitis B or C. Comparable exposure and pharmacokinetic profiles were seen in cirrhotic (Child-Pugh Grade A) and non-cirrhotic patients.

Site of administration
Subcutaneous administration of Pegasys should be limited to the abdomen and thigh, as the extent of absorption based on AUC was about 20% to 30% higher upon injection in the abdomen and thigh. Exposure to Pegasys was decreased in studies following administration of Pegasys in the arm compared to administration in the abdomen and thigh.

5.3 Preclinical safety data

The non-clinical toxicity studies conducted with Pegasys were limited due to species specificity of interferons. Acute and chronic toxicity studies have been carried out in cynomolgus monkeys, and the findings observed in peginterferon dosed animals were similar in nature to those produced by interferon alfa-2a.

Reproductive toxicity studies have not been performed with Pegasys. As with other alfa interferons, prolongation of the menstrual cycle was observed following administration of peginterferon alfa-2a to female monkeys. Treatment with interferon alfa-2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys. Although no teratogenic effects were seen in the offspring delivered at term, adverse effects in humans cannot be excluded.

Pegasys plus ribavirin
When used in combination with ribavirin, Pegasys did not cause any effects in monkeys not previously seen with either active substance alone. The major treatment-related change was reversible mild to

moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Polysorbate 80
Benzyl alcohol
Sodium acetate
Acetic acid
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

Pegasys 135 micrograms solution for injection
3 years.

Pegasys 180 micrograms solution for injection
4 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

1 ml of solution for injection in vial (Type I glass) with stopper (rubber butyl). Available in packs of 1 or 4 vials. Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

The solution for injection is for single use only. It should be inspected visually for particulate matter and discoloration before administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

Pegasys 135 micrograms solution for injection
EU/1/02/221/001
EU/1/02/221/002

Pegasys 180 micrograms solution for injection
EU/1/02/221/003
EU/1/02/221/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2002
Date of latest renewal: 20 June 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 90 micrograms solution for injection in pre-filled syringe
Pegasys 135 micrograms solution for injection in pre-filled syringe
Pegasys 180 micrograms solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pegasys 90 micrograms solution for injection in pre-filled syringe
Each syringe of 0.5 ml solution contains 90 micrograms peginterferon alfa-2a*.

Pegasys 135 micrograms solution for injection in pre-filled syringe
Each syringe of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a*.

Pegasys 180 micrograms solution for injection in pre-filled syringe
Each syringe of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a*.

The strength indicates the quantity of the interferon alfa-2a moiety of peginterferon alfa-2a without consideration of the pegylation.

*The active substance, peginterferon alfa-2a, is a covalent conjugate of the protein interferon alfa-2a produced by recombinant DNA technology in *Escherichia coli* with bis-[monomethoxy polyethylene glycol].

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1.

Excipient with known effect: Benzyl alcohol (10 mg/ 1 ml)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is clear and colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B

Pegasys is indicated for the treatment of hepatitis B envelope antigen (HBeAg)-positive or HBeAg-negative-chronic hepatitis B (CHB) in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis (see sections 4.4 and 5.1).

Chronic hepatitis C

Adult patients

Pegasys is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC) in patients with compensated liver disease (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.2 and 5.1.

Paediatric patients 5 years of age and older:
Pegasys in combination with ribavirin is indicated for the treatment of chronic hepatitis C in treatment-naïve children and adolescents 5 years of age and older who are positive for serum HCV-RNA.

When deciding to initiate treatment in childhood, it is important to consider growth inhibition induced by combination therapy. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

4.2 Posology and method of administration

Treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis B or C.

Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Pegasys.
Monotherapy for hepatitis C should only be considered in cases of contraindication to other medicinal products.

Posology

Chronic hepatitis B – adult patients

The recommended dosage and duration of Pegasys for both HBeAg-positive and HBeAg-negative chronic hepatitis B is 180 micrograms once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

Chronic hepatitis C – treatment-naïve adult patients

The recommended dose for Pegasys is 180 micrograms once weekly by subcutaneous administration in the abdomen or thigh given in combination with oral ribavirin or as monotherapy.

The dose of ribavirin to be used in combination with Pegasys is given in Table 1.
The ribavirin dose should be administered with food.

Duration of treatment–dual therapy with Pegasys and ribavirin

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 regardless of pre-treatment viral load should receive 48 weeks of therapy.
Treatment for 24 weeks may be considered in patients infected with

- genotype 1 with low viral load (LVL) (≤ 800,000 IU/ml) at baseline or
- genotype 4

who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1). In these patients, tolerability to combination therapy and additional prognostic factors such as degree of fibrosis should be taken into account when deciding on treatment duration. Shortening the treatment duration in patients with genotype 1 and high viral load (HVL) (>800, 000 IU/ml) at baseline who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24 should be considered with even more caution since the limited data available suggest that this may significantly negatively impact the sustained virologic response.

Patients infected with HCV genotype 2 or 3 who have detectable HCV RNA at week 4, regardless of pre-treatment viral load should receive 24 weeks of therapy. Treatment for only 16 weeks may be

considered in selected patients infected with genotype 2 or 3 with LVL (≤ 800,000 IU/ml) at baseline who become HCV negative by week 4 of treatment and remains HCV negative by week 16. Overall 16 weeks of treatment may be associated with a lower chance of response and is associated with a higher risk of relapse than a 24 week treatment duration (see section 5.1). In these patients, tolerability to combination therapy and the presence of additional clinical or prognostic factors such as degree of fibrosis should be taken into account when considering deviations from standard 24 weeks treatment duration. Shortening the treatment duration in patients infected with genotype 2 or 3 with HVL (> 800,000 IU/ml) at baseline who become HCV negative by week 4 should be considered with more caution as this may significantly negatively impact the sustained virological response (see Table 1).

Available data for patients infected with genotype 5 or 6 are limited; therefore combination treatment with 1,000/1,200 mg of ribavirin for 48 weeks is recommended.

Table 1: Dosing recommendations for combination therapy for HCV patients

Genotype	Pegasys dose	Ribavirin dose	Duration
Genotype 1 LVL with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 4 with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 2 or 3 without RVR**	180 micrograms	800 mg	24 weeks
Genotype 2 or 3 LVL with RVR**	180 micrograms	800 mg[(a)]	16 weeks[(a)] or 24 weeks
Genotype 2 or 3 HVL with RVR**	180 micrograms	800 mg	24 weeks

*RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24;
**RVR = rapid viral response (HCV RNA negative) by week 4
LVL = ≤ 800,000 IU/ml; HVL = > 800,000 IU/ml
[(a)] It is presently not clear whether a higher dose of ribavirin (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The ultimate clinical impact of a shortened initial treatment of 16 weeks instead of 24 weeks is unknown, taking into account the need for re-treating non-responding and relapsing patients.

The recommended duration of Pegasys monotherapy is 48 weeks.

Chronic hepatitis C – treatment-experienced adult patients

The recommended dose of Pegasys in combination with ribavirin is 180 mcg once weekly by subcutaneous administration. For patients <75 kg and ≥75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, and regardless of genotype, should be administered.
Patients who have detectable virus at week 12 should stop therapy. The recommended total duration of therapy is 48 weeks. If patients infected with virus genotype 1, not responding to prior treatment with peginterferon and ribavirin are considered for treatment, the recommended total duration of therapy is 72 weeks (see section 5.1).

HIV-HCV co-infected adult patients

The recommended dosage for Pegasys, alone or in combination with ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks. For patients infected with HCV genotype 1 <75 kg and ≥75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, should be administered. Patients infected with HCV genotypes other than genotype 1 should receive 800 mg daily of ribavirin. A duration of therapy less than 48 weeks has not been adequately studied.

Duration of therapy when Pegasys is used in combination with other medicinal products

Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Pegasys.

Predictability of response and non-response with Pegasys and ribavirin dual therapy– treatment-naïve patients

Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see Tables 2 and 12).

Table 2: Predictive value of week 12 virological response at the recommended dosing regimen while on Pegasys combination therapy

Genotype	**Negative**			**Positive**		
	No response by week 12	No sustained response	Predictive Value	Response by week 12	Sustained response	Predictive Value
Genotype 1 (N= 569)	102	97	**95%** (97/102)	467	271	**58%** (271/467)
Genotype 2 and 3 (N=96)	3	3	**100%** (3/3)	93	81	**87%** (81/93)

The negative predictive value for sustained response in patients treated with Pegasys in monotherapy was 98%.
A similar negative predictive value has been observed in HIV-HCV co-infected patients treated with Pegasys monotherapy or in combination with ribavirin (100% (130/130) or 98% (83/85), respectively). Positive predictive values of 45% (50/110) and 70% (59/84) were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Predictability of response and non-response with Pegasys and ribavirin dual therapy – treatment-experienced patients

In non-responder patients re-treated for 48 or 72 weeks, viral suppression at week 12 (undetectable HCV RNA defined as <50 IU/ml) has been shown to be predictive for sustained virological response. The probabilities of not achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was not achieved at week 12 were 96% (363 of 380) and 96% (324 of 339), respectively. The probabilities of achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was achieved at week 12 were 35% (20 of 57) and 57% (57 of 100), respectively.

Dose adjustment for adverse reactions in adult patients

General
Where dose adjustment is required for moderate to severe adverse reactions (clinical and/or laboratory) initial dose reduction to 135 micrograms is generally adequate for adult patients. In some cases, dose reduction to 90 micrograms or 45 micrograms is necessary. Dose increases to or towards the original dose may be considered when the adverse reaction abates (see sections 4.4 and 4.8).

Haematological (see also Table 3)
For adults, dose reduction is recommended if the neutrophil count is < 750/mm^3. For patients with Absolute Neutrophil Count (ANC) < 500/mm^3 treatment should be suspended until ANC values return to > 1000/mm^3. Therapy should initially be re-instituted at 90 micrograms Pegasys and the neutrophil count monitored. Guidance for dose reduction based on ANC levels for paediatric patients is provided in Table 7.

Dose reduction to 90 micrograms is recommended if the platelet count is < 50,000/mm^3. Cessation of therapy is recommended when platelet count decreases to levels < 25,000/mm^3.

Specific recommendations for management of treatment-emergent anaemia in adults are as follows: ribavirin should be reduced to 600 milligrams/day (200 milligrams in the morning and 400 milligrams in the evening) if either of the following apply: (1) a patient without significant cardiovascular disease experiences a fall in haemoglobin to < 10 g/dl and ≥ 8.5 g/dl, or (2) a patient with stable cardiovascular disease experiences a fall in haemoglobin by ≥ 2 g/dl during any 4 weeks of treatment. A return to original dosing is not recommended. Ribavirin should be discontinued if either of the following applies: (1) a patient without significant cardiovascular disease experiences a fall in haemoglobin confirmed to < 8.5 g/dl; (2) a patient with stable cardiovascular disease maintains a haemoglobin value < 12 g/dl despite 4 weeks on a reduced dose. If the abnormality is reversed, ribavirin may be restarted at 600 milligrams daily, and further increased to 800 milligrams daily at the discretion of the treating physician. A return to original dosing is not recommended.

Table 3: Dose adjustment for adverse reaction (for further guidance see also text above)

	Reduce ribavirin to 600 mg	Withhold ribavirin	Reduce Pegasys to 135/90/45 micrograms	Withhold Pegasys	Discontinue combination
Absolute Neutrophil Count			< 750/mm^3	< 500/mm^3	
Platelet Count			< 50,000/mm^3 > 25,000/mm^3		< 25,000/mm^3
Haemoglobin - no cardiac disease	< 10 g/dl, and ≥ 8.5 g/dl	< 8.5 g/dl			
Haemoglobin - stable cardiac disease	decrease ≥ 2 g/dl during any 4 weeks	< 12 g/dl despite 4 weeks at reduced dose			

In case of intolerance to ribavirin, Pegasys monotherapy should be continued.

Liver function
Fluctuations in abnormalities of liver function tests are common in patients with chronic hepatitis C. Increases in ALT levels above baseline (BL) have been observed in patients treated with Pegasys, including patients with a virological response.
In chronic hepatitis C clinical trials with adult patients, isolated increases in ALT (≥ 10x ULN, or ≥ 2x BL for patients with a BL ALT ≥ 10x ULN) which resolved without dose-modification were observed in 8 of 451 patients treated with combination therapy. If ALT increase is progressive or persistent, the dose should be reduced initially to 135 micrograms. When increases in ALT levels are progressive despite dose reduction, or are accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see section 4.4). Guidance for dose reduction based on ALT levels for paediatric patients is provided in Table 7.

For chronic hepatitis B patients, transient flares of ALT levels sometimes exceeding 10 times the upper limit of normal are not uncommon, and may reflect immune clearance. Treatment should normally not be initiated if ALT is >10 times the upper limit of normal. Consideration should be given to continuing treatment with more frequent monitoring of liver function during ALT flares. If the Pegasys dose is reduced or withheld, therapy can be restored once the flare is subsiding (see section 4.4).

Special populations

Elderly
Adjustments in the recommended dosage of 180 micrograms once weekly are not necessary when instituting Pegasys therapy in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is required for adult patients with mild or moderate renal impairment. A reduced dose of 135 mcg once weekly is recommended in adult patients with severe renal impairment or end stage renal disease (see section 5.2). Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of Pegasys during the course of therapy should be made in the event of adverse reactions.

Hepatic impairment
In patients with compensated cirrhosis (e.g., Child-Pugh A), Pegasys has been shown to be effective and safe. Pegasys has not been evaluated in patients with decompensated cirrhosis (e.g., Child-Pugh B or C or bleeding oesophageal varices) (see section 4.3).

The Child-Pugh classification divides patients into groups A, B, and C, or "Mild", "Moderate" and "Severe" corresponding to scores of 5-6, 7-9 and 10-15, respectively.

Modified Assessment

Assessment	Degree of abnormality	Score
Encephalopathy	None Grade 1-2 Grade 3-4*	1 2 3
Ascites	Absent Slight Moderate	1 2 3
S-Bilirubin (mg/dl)	<2 2.0-3 >3	1 2 3
SI unit = μmol/l)	<34 34-51 >51	1 2 3
S-Albumin (g/dl)	>3.5 3.5-2.8 <2.8	1 2 3
INR	<1.7 1.7-2.3 >2.3	1 2 3

*Grading according to Trey, Burns and Saunders (1966)

Paediatric population

Pegasys is contraindicated in neonates and young children up to 3 years old due to the excipient benzyl alcohol (see sections 4.3 and 4.4).

For children and adolescents aged 5 to 17 years with chronic hepatitis C, and having a Body Surface Area (BSA) greater than 0.7 m^2, the recommended doses for Pegasys and ribavirin are provided in Table 4 and Table 5. It is recommended that Pegasys pre-filled syringes be used for paediatric patients. The Pegasys pre-filled pens do not allow for appropriate adjustment of dosing in these patients. Patients who initiate treatment prior to their 18^{th} birthday should maintain paediatric dosing through the completion of therapy.

Pegasys should not be used in children with a Body Surface Area (BSA) less than 0.71 as there is no available data for this subpopulation.

To calculate BSA, it is recommended to use Mosteller's equation:

$$BSA\ (m^2) = \sqrt{\left(\frac{Height\ (cm) \times Weight\ (kg)}{3600}\right)}$$

Duration of treatment
The duration of treatment with Pegasys in combination with ribavirin in paediatric patients with chronic hepatitis C depends on viral genotype. Patients infected with viral genotypes 2 or 3 should receive 24 weeks of treatment, while patients infected with any other genotype should receive 48 weeks of therapy.

Patients who still have detectable levels of HCV-RNA despite an initial 24 weeks of therapy, should discontinue therapy, as it is unlikely they will be able to achieve a sustained virological response with continued therapy.

Table 4: Pegasys dosing recommendations for paediatric patients aged 5 to 17 years

Body Surface Area (BSA) range (m^2)	Weekly dose (mcg)
0.71-0.74	65
0.75-1.08	90
1.09-1.51	135
>1.51	180

For children and adolescents aged 5 to 17 years with chronic hepatitis C, the recommended dose of ribavirin is based on the patient's body weight, with a target dose of 15 mg/kg/day, divided in two daily doses. For children and adolescents 23 kg or greater, a dosing schedule using 200 mg ribavirin tablets is provided in Table 5. Patients and caregivers must not attempt to break the 200 mg tablets.

Table 5: Ribavirin dosing recommendations for paediatric patients aged 5 to 17 years

Body weight kg (lbs)	Ribavirin daily dose (Approx. 15 mg/kg/day)	Ribavirin number of tablets
23 – 33 (51-73)	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
34 – 46 (75-101)	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
47 – 59 (103-131)	800 mg/day	2 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
60 – 74 (132-163)	1000 mg/day	2 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.
≥75 (>165)	1200 mg/day	3 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.

Dose adjustment for adverse reactions in paediatric patients

For paediatric patients, based on toxicities (see Table 6), up to three levels of dose modification can be made before dose interruption or discontinuation is considered.

Table 6: Pegasys dose modification recommendations in paediatric patients

Starting dose (mcg)	**1 level reduction (mcg)**	**2 level reduction (mcg)**	**3 level reduction (mcg)**
65	45	30	20
90	65	45	20
135	90	65	30
180	135	90	45

If toxicities occur which may be related to Pegasys and/or ribavirin administration, the dose of one or both medicinal products can be reduced. Additionally, ribavirin or Pegasys plus ribavirin combination therapy can be discontinued. It is important to note that ribavirin should never be given as monotherapy. Recommendations for dose modifications for toxicities known to have an association with Pegasys administration that are specific for the paediatric population are presented in Table 7. Unless otherwise noted, the management of all other toxicities should follow the adult recommendations.

Table 7: Pegasys dose modification recommendations for toxicities in paediatric patients

Toxicity	Pegasys dose modification
Neutropenia	750-999 cells/mm^3: Week 1-2 - immediate 1 level adjustment; Week 3-48: no modification. 500-749 cells/mm^3: Week 1-2 - interrupt dosing until >750 cells/mm^3 then resume dose with a 1 level adjustment, assess weekly for the next 3 weeks to verify ANC >750 cells/mm^3; Week 3-48 - immediate 1 level adjustment. 250-499 cells/mm^3: Week 1-2 - interrupt dosing until >750 cells/mm^3 then resume dose with a 2 level adjustment; Week 3-48 - interrupt dosing until >750 cells/mm^3 then resume dose with a 1 level adjustment. < 250 cells/mm^3 (or febrile neutropenia) discontinue treatment.
Increased alanine transaminase (ALT)	For persistent or increasing elevations ≥5 but <10 x ULN, reduce dose with a 1 level adjustment and monitor weekly ALT level to ensure it is stable or decreasing For persistent ALT values ≥10 x ULN discontinue treatment.

In paediatric patients, ribavirin treatment-associated toxicities, such as treatment-emergent anaemia, will be managed by reduction of the full dose. The dose reduction levels are provided in Table 8.

Table 8: Ribavirin dose modification recommendations in paediatric patients

Full dose (Approx. 15 mg/kg/day)	**One step dose modification** (Approx. 7.5 mg/kg/day)	**Ribavirin number of tablets**
400 mg/day	200 mg/day	1 x 200 mg tablets A.M.
600 mg/day	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
800 mg/day	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
1000 mg/day	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
1200 mg/day	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.

There is limited experience with Pegasys in treating paediatric patients with HCV aged 3 to 5 years, or who have failed to be adequately treated previously. There are no data in paediatric patients coinfected with HCV/HIV or with renal impairment.

Method of administration

Pegasys is administered subcutaneously in the abdomen or thigh. Exposure to Pegasys was decreased in studies following administration of Pegasys in the arm (see section 5.2).

Pegasys is designed for administration by the patient or carer. Each syringe should be used by one person only and is for single use.

Appropriate training is recommended for non-healthcare professionals administering this medicinal product. The “Instructions for the User”, provided in the carton, must be followed carefully by the patient.

4.3 Contraindications

- Hypersensitivity to the active substance, to alfa interferons, or to any of the excipients listed in section 6.1
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4)
- HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6, except if only due to indirect hyperbilirubinemia caused by medicinal products such as atazanavir and indinavir
- Combination with telbivudine (see section 4.5)
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol (see section 4.4 for benzyl alcohol)
- In paediatric patients, the presence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Pegasys therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alfa interferons. All patients should be closely monitored for any signs or symptoms of psychiatric disorders. If symptoms of psychiatric disorders 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, it is recommended that treatment with Pegasys be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions: If treatment with Pegasys is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
The use of Pegasys in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

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 alfa interferon. If treatment with alfa 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.

Growth and development (children and adolescents): During the course of Pegasys plus ribavirin therapy lasting up to 48 weeks in patients aged 5 to 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1).

The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials on a case by case basis (see sections 4.8 and 5.1).

- It is important to consider that the combination therapy induced a growth inhibition during treatment, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

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

Laboratory tests prior to and during therapy

Prior to beginning Pegasys 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 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 (including glucose monitoring).

In clinical trials, Pegasys treatment was associated with decreases in both total white blood cell (WBC) count and absolute neutrophil count (ANC), usually starting within the first 2 weeks of treatment (see section 4.8). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see section 4.2), reached normal values by 8 weeks in the majority of patients and returned to baseline in all patients after about 16 weeks.

Pegasys treatment has been associated with decreases in platelet count, which returned to pre-treatment levels during the post-treatment observation period (see section 4.8). In some cases, dose modification may be necessary (see section 4.2).

The occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 15% of chronic hepatitis C patients in clinical trials on the combined treatment of Pegasys with ribavirin. The frequency depends on the treatment duration and the dose of ribavirin (see section 4.8). The risk of developing anaemia is higher in the female population.

Caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a peginterferon and ribavirin concomitantly with azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon re-introduction of either treatment alone (see section 4.5).

The use of Pegasys 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 haematological adverse reactions. 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 alfa interferons, including Pegasys. Prior to initiation of Pegasys therapy, TSH and T4 levels should be evaluated. Pegasys treatment may be initiated or continued if TSH levels can be maintained in the normal range by pharmaceutical means. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see section 4.8). Hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Pegasys (see section 4.8). Patients with these conditions who cannot be effectively controlled by medication should not begin Pegasys monotherapy or Pegasys/ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Pegasys or Pegasys/ribavirin therapy.

Cardiovascular system
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alfa interferon therapies, including Pegasys. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of Pegasys 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 (see section 4.2).

Liver function
In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. Increases in ALT levels above baseline have been observed in patients treated with Pegasys, including patients with a viral response. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued (see sections 4.2 and 4.8).

In chronic hepatitis B, unlike chronic hepatitis C, disease exacerbations during therapy are not uncommon and are characterised by transient and potentially significant increases in serum ALT. In clinical trials with Pegasys in HBV, marked transaminase flares have been accompanied by mild changes in other measures of hepatic function and without evidence of hepatic decompensation. In approximately half the cases of flares exceeding 10 times the upper limit of normal, Pegasys dosing was reduced or withheld until the transaminase elevations subsided, while in the rest therapy was continued unchanged. More frequent monitoring of hepatic function was recommended in all instances.

Hypersensitivity
Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alfa 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 alfa 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 re-assessed (see also *Endocrine system* in sections 4.4 and 4.8).

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 (see section 4.8).

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 alfa interferons including Pegasys. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

Ocular changes
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 Pegasys. 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. Adult and paediatric patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during Pegasys therapy. Pegasys treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Pulmonary changes
Pulmonary symptoms, including dyspnoea, pulmonary infiltrates, pneumonia, and pneumonitis have been reported during therapy with Pegasys. In case of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.

Skin disorder
Use of alfa interferons has been associated with exacerbation or provocation of psoriasis and sarcoidosis. Pegasys 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 Pegasys and ribavirin treatment have not been established in patients with liver and other transplantations. Liver and renal graft rejections have been reported with Pegasys, alone or in combination with ribavirin.

HIV-HCV coinfection
Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with Pegasys with or without ribavirin. In study NR15961, patients concurrently treated with stavudine and interferon therapy with or without ribavirin, the incidence of pancreatitis and/or lactic acidosis was 3% (12/398).

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

Co-infected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with ribavirin in combination with interferons, including Pegasys. Baseline variables in co-infected cirrhotic patients that may be associated with hepatic decompensation include: increased serum bilirubin, decreased haemoglobin, increased alkaline phosphatase or decreased platelet count, and treatment with didanosine (ddI).

The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

During treatment, co-infected patients should be closely monitored for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function; e.g., Child-Pugh score of 7 or greater). The Child-Pugh scoring may be affected by factors related to treatment (i.e. indirect hyperbilirubinemia, decreased albumin) and not necessarily

attributable to hepatic decompensation. Treatment with Pegasys should be discontinued immediately in patients with hepatic decompensation.

In patients co-infected with HIV-HCV, limited efficacy and safety data are available in patients with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Pegasys and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Pegasys 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.

Use of peginterferon as long term maintenance monotherapy (unapproved use)
In a randomised, controlled US study (HALT-C) of HCV non-responder patients with varied degrees of fibrosis where 3.5 years of treatment with 90 micrograms/week of Pegasys monotherapy was studied, no significant reductions were observed in the rate of fibrosis progression or related clinical events.

Excipient
Pegasys contains benzyl alcohol. Must not be given to premature babies or neonates. May cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Administration of Pegasys 180 micrograms once weekly for 4 weeks in healthy male subjects did not show any effect on mephenytoin, dapsone, debrisoquine and tolbutamide pharmacokinetics profiles, suggesting that Pegasys has no effect on *in vivo* metabolic activity of cytochrome P450 3A4, 2C9, 2C19 and 2D6 isozymes.

In the same study, a 25% increase in the AUC of theophylline (marker of cytochrome P450 1A2 activity) was observed, demonstrating that Pegasys is an inhibitor of cytochrome P450 1A2 activity. Serum concentrations of theophylline should be monitored and appropriate dose adjustments of theophylline made for patients taking theophylline and Pegasys concomitantly. The interaction between theophylline and Pegasys is likely to be maximal after more than 4 weeks of Pegasys therapy.

HCV monoinfected patients and HBV monoinfected patients

In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95 mg; range 30 mg to 150 mg), treatment with Pegasys 180 micrograms sc once weekly for 4 weeks was associated with mean methadone levels that were 10% to 15% higher than at baseline. The clinical significance of this finding is unknown; nonetheless, patients should be monitored for the signs and symptoms of methadone toxicity. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of peginterferon alfa-2a and ribavirin concomitantly with azathioprin should be avoided. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicinal products should be stopped (see section 4.4).

Results from pharmacokinetic substudies of pivotal phase III trials demonstrated no pharmacokinetic interaction of lamivudine on Pegasys in HBV patients or between Pegasys and ribavirin in HCV patients.

A clinical trial investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration for the treatment of HBV, indicates that the combination is associated with an increased risk for developing peripheral neuropathy. The mechanism behind these events is not known; thus, co-treatment with telbivudine and other interferons (pegylated or standard) may also entail an excess risk. Moreover, the benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established. Therefore, the combination of Pegasys with telbivudine is contraindicated (see section 4.3).

HIV-HCV co-infected patients
No apparent evidence of drug interaction was observed in 47 HIV-HCV co-infected patients who completed a 12 week pharmacokinetic substudy to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine and zidovudine or stavudine). However, due to high variability, the confidence intervals were quite wide. Plasma exposure of ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).

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 (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral therapy regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of peginterferon alfa-2a in pregnant women. Studies in animals with interferon alfa-2a have shown reproductive toxicity (see section 5.3) and the potential risk for humans is unknown. Pegasys is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

It is unknown whether peginterferon alfa-2a/metabolites are excreted in human milk. Because of the potential for adverse reactions in breastfed infants, breastfeeding should be discontinued prior to initiation of treatment.

Fertility

There are no data on the effects of peginterferon alfa-2a on fertility in women. A prolongation of the menstrual cycle has been seen with peginterferon alfa-2a in female monkeys (see section 5.3).

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 Pegasys in

combination with ribavirin. Female patients of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded. Please refer to the ribavirin SmPC.

4.7 Effects on ability to drive and use machines

Pegasys has 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.

4.8 Undesirable effects

Summary of the safety profile

Chronic hepatitis C

The frequency and severity of the most commonly reported adverse reactions with Pegasys are similar to those reported with interferon alfa-2a (see Table 9). The most frequently reported adverse reactions with Pegasys 180 micrograms were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy.

Chronic hepatitis B

In clinical trials of 48 weeks treatment and 24 weeks follow-up, the safety profile for Pegasys in chronic hepatitis B was similar to that seen in chronic hepatitis C. With the exception of pyrexia the frequency of the majority of the reported adverse reactions was notably less in CHB patients treated with Pegasys monotherapy compared with HCV patients treated with Pegasys monotherapy (see Table 9). Adverse events were experienced by 88% of Pegasys-treated patients as compared with 53% of patients in the lamivudine comparator group, while 6% of the Pegasys-treated and 4% of the lamivudine-treated patients experienced serious adverse events during the studies. Adverse events or laboratory abnormalities led to 5% of patients withdrawing from Pegasys treatment, while less than 1% of patients withdrew from lamivudine treatment for these reasons. The percentage of patients with cirrhosis who withdrew from treatment was similar to that of the overall population in each treatment group.

Chronic hepatitis C in prior non-responder patients

Overall, the safety profile for Pegasys in combination with ribavirin in prior non-responder patients was similar to that in naïve patients. In a clinical trial of non-responder patients to prior pegylated interferon alfa-2b/ribavirin, which exposed patients to either 48 or 72 weeks of treatment, the frequency of withdrawal for adverse events or laboratory abnormalities from Pegasys treatment and ribavirin treatment was 6% and 7%, respectively, in the 48 week arms and 12% and 13% ,respectively, in the 72 week arms. Similarly for patients with cirrhosis or transition to cirrhosis, the frequencies of withdrawal from Pegasys treatment and ribavirin treatment were higher in the 72-week treatment arms (13% and 15%) than in the 48-week arms (6% and 6%). Patients who withdrew from previous therapy with pegylated interferon alfa-2b/ribavirin because of haematological toxicity were excluded from enrolling in this trial.

In another clinical trial, non-responder patients with advanced fibrosis or cirrhosis (Ishak score of 3 to 6) and baseline platelet counts as low as 50,000/mm^3 were treated for 48 weeks. Haematologic laboratory abnormalities observed during the first 20 weeks of the trial included anaemia (26% of patients experienced a haemoglobin level of <10 g/dl), neutropenia (30% experienced an ANC <750/mm^3), and thrombocytopenia (13% experienced a platelet count <50,000/ mm^3) (see section 4.4).

Chronic hepatitis C and HIV co-infection

In HIV-HCV co-infected patients, the clinical adverse reaction profiles reported for Pegasys, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients For HIV-HCV patients receiving Pegasys and ribavirin combination therapy other undesirable effects have been reported in ≥ 1% to ≤ 2% of patients: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia. Pegasys treatment was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of Pegasys had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data are available in co-infected patients with CD4+ cell counts <200/µl.

Tabulated list of adverse reactions

Table 9 summarises the undesirable effects reported with Pegasys monotherapy in CHB or CHC patients and with Pegasys in combination with ribavirin in CHC patients. Undesirable effects reported in clinical studies are grouped according to frequency as follows: 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). For spontaneous reports of undesirable effects from post-marketing experience, the frequency is not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

Table 9: Undesirable effects reported with Pegasys monotherapy for HBV or HCV or in combination with ribavirin for HCV patients in clinical trials and post marketing

Body system	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Infections and infestations		Bronchitis, upper respiratory infection, oral candidiasis, herpes simplex, fungal, viral and bacterial infections	Pneumonia, skin infection	Endocarditis, otitis externa		Sepsis
Neoplasms benign and malignant			Hepatic neoplasm			
Blood and lymphatic system disorders		Thrombocytopenia, anaemia, lymphadenopathy		Pancytopenia	Aplastic anaemia	Pure red cell aplasia
Immune system disorders			Sarcoidosis, thyroiditis	Anaphylaxis, systemic lupus erythematosus rheumatoid arthritis	Idiopathic or thrombotic thrombocytopenic purpura	Liver and renal graft rejection, Vogt-Koyanagi-Harada disease
Endocrine disorders		Hypothyroidism, hyperthyroidism	Diabetes	Diabetic ketoacidosis		
Metabolism and nutrition disorders	Anorexia		Dehydration			

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Psychiatric disorders	Depression*, anxiety, insomnia*	Aggression, mood alteration, emotional disorders, nervousness, libido decreased	Suicidal ideation, hallucinations	Suicide, psychotic disorder		Mania, bipolar disorders, homicidal ideation
Nervous system disorders	Headache, dizziness*, concentration impaired	Syncope, migraine, memory impairment, weakness, hypoaesthesia, hyperaesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence	Peripheral neuropathy	Coma, convulsions, facial palsy		Cerebral ischaemia
Eye disorders		Vision blurred, eye pain, eye inflammation, xerophthalmia	Retinal haemorrhage	Optic neuropathy, papilloedema, retinal vascular disorder, retinopathy, corneal ulcer	Vision loss	Serous retinal detachment
Ear and labyrinth disorders		Vertigo, earache	Hearing loss			
Cardiac disorders		Tachycardia, oedema peripheral, palpitations		Myocardial infarction, congestive heart failure, cardiomyopathy, angina, arrhythmia, atrial fibrillation, pericarditis, supraventricular tachycardia		
Vascular disorders		Flushing	Hypertension	Cerebral haemorrhage, vasculitis		Peripheral ischaemia
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		Pulmonary arterial hypertension[§]

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Gastrointestinal disorders	Diarrhoea*, nausea*, abdominal pain*	Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, dry mouth	Gastrointestinal bleeding	Peptic ulcer, pancreatitis		Ischaemic colitis, tongue pigmentation
Hepato-biliary disorders			Hepatic dysfunction	Hepatic failure, cholangitis, fatty liver		
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, pruritis, dry skin	Psoriasis, urticaria, eczema, rash, sweating increased, skin disorder, photosensitivity reaction, night sweats			Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, erythema multiforme	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps		Myositis		Rhabdomyolysis
Renal and urinary disorders				Renal insufficiency		
Reproductive system and breast disorders		Impotence				
General disorders and administration site conditions	Pyrexia, rigors*, pain*, asthenia, fatigue, injection site reaction*, irritability*	Chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst				
Investigations		Weight decreased				
Injury, poisoning and procedural complications				Substance overdose		

*These adverse reactions were common (**≥1/100 to < 1/10)** in CHB patients treated with Pegasys monotherapy

§ Class label for interferon products, see below Pulmonary arterial hypertension.

Description of selected adverse reactions

Pulmonary arterial hypertension
Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

Laboratory values
Pegasys treatment was associated with abnormal laboratory values: ALT increase, bilirubin increase, electrolyte disturbance (hypokalaemia, hypocalcaemia, hypophosphataemia), hyperglycaemia, hypoglycaemia and elevated triglycerides (see section 4.4.). With both Pegasys monotherapy, and also the combined treatment with ribavirin, up to 2% of patients experienced increased ALT levels that led to dose modification or discontinuation of the treatment.

Treatment with Pegasys was associated with decreases 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 (see sections 4.2 and 4.4).

Moderate (ANC: 0.749 - 0.5 x 10^9/l) and severe (ANC: < 0.5 x 10^9/l) neutropenia was observed respectively in 24% (216/887) and 5% (41/887) of patients receiving Pegasys 180 micrograms and ribavirin 1000/1200 milligrams for 48 weeks.

Anti-interferon antibodies
1-5% of patients treated with Pegasys developed neutralising anti-interferon antibodies. As with other interferons, a higher incidence of neutralising antibodies was seen in chronic hepatitis B. However in neither disease was this correlated with lack of therapeutic response.

Thyroid function
Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see section 4.4). The frequencies observed (4.9%) in patients receiving Pegasys/ribavirin (NV15801) are similar to those observed with other interferons.

Laboratory values for HIV-HCV co-infected patients
Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment. Decrease in ANC levels below 500 cells/mm^3 was observed in 13% and 11% of patients receiving Pegasys monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm^3 was observed in 10% and 8% of patients receiving Pegasys monotherapy and combination therapy, respectively. Anaemia (haemoglobin < 10 g/dl) was reported in 7% and 14% of patients treated with Pegasys monotherapy or in combination therapy, respectively.

Paediatric population

Chronic hepatitis C

In a clinical trial with 114 paediatric patients (5 to 17 years of age) treated with Pegasys alone or in combination with ribavirin (see section 5.1), dose modifications were required in approximately one-third of patients, most commonly for neutropenia and anaemia. In general, the safety profile observed in paediatric patients was similar to that seen in adults. In the paediatric study, the most prevalent adverse reactions in patients treated with combination therapy for up to 48 weeks with Pegasys and ribavirin were influenza-like illness (91%), headache (64%), gastrointestinal disorder (56%), and injection-site reaction (45%). A full listing of adverse reactions reported in this treatment group (n=55) is provided in Table 10. Seven patients receiving combination Pegasys and ribavirin treatment for 48 weeks discontinued therapy for safety reasons (depression, psychiatric evaluation abnormal, transient

blindness, retinal exudates, hyperglycaemia, type 1 diabetes mellitus, and anaemia). Most of the adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 2 patients in the Pegasys plus ribavirin combination therapy group (hyperglycaemia and cholecystectomy).

Table 10: Adverse reactions reported among paediatric patients infected with HCV and assigned to Pegasys plus ribavirin in study NV17424

Body system	Very common	Common
Infections and infestations		Infectious mononucleosis, pharyngitis streptococcal, influenza, gastroenteritis viral, candidiasis, gastroenteritis, tooth abscess, hordeolum, urinary tract infection, nasopharyngitis
Blood and lymphatic system disorders		Anaemia
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia, type 1 diabetes mellitus
Psychiatric disorders	Insomnia	Depression, anxiety, hallucination, abnormal behaviour, aggression, anger, attention deficit / hyperactivity disorder
Nervous system disorders	Headache	Dizziness, disturbance in attention, migraine
Eye disorders		Blindness transient, retinal exudates, visual impairment, eye irritation, eye pain, eye pruritis
Ear and labyrinth disorders		Ear pain
Respiratory, thoracic and mediastinal disorders		Dyspnoea, epistaxis
Gastrointestinal disorders	Gastrointestinal disorder	Abdominal pain upper, stomatitis, nausea, aphthous stomatitis, oral disorder
Skin and subcutaneous tissue disorders	Rash, pruritus, alopecia	Swollen face, drug eruption
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Back pain, pain in extremity
Renal and urinary disorders		Dysuria, incontinence, urinary tract disorder
Reproductive system and breast disorders		Vaginal discharge
General disorders and administration site conditions	Influenza-like illness, injection site reaction, irritability, fatigue	Pyrexia, vessel puncture site haematoma, pain
Investigations		Psychiatric evaluation abnormal
Surgical and medical procedures		Tooth extraction, cholecystectomy
Social circumstances		Educational problem

Growth inhibition was observed in paediatric patients (see section 4.4). Paediatric patients treated with Pegasys plus ribavirin combination therapy showed a delay in weight and height increases after 48 weeks of therapy compared with baseline. Patient ‘weight for age’ and ‘height for age’ percentiles of the normative population decreased during treatment. At the end of 2 years follow-up after treatment, most patients had returned to baseline normative growth curve percentiles for weight and height (mean weight percentile was 64% at baseline and 60% at 2 years post-treatment; mean height percentile was 54% at baseline and 56% at 2 years post-treatment). At the end of treatment, 43% of patients experienced a weight percentile decrease of 15 percentiles or more, and 25% (13 of 53) experienced a height percentile decrease of 15 percentiles or more on the normative growth curves. At 2 years post-treatment, 16% (6 of 38) of patients remained 15 percentiles or more below their baseline weight curve and 11% (4 of 38) remained 15 percentiles or more below their baseline height curve.

55% (21 of 38) of subjects who completed the original study enrolled in the long-term follow up extending up to 6 years post-treatment. The study demonstrated that the post-treatment recovery in growth at 2 years post-treatment was maintained to 6 years post-treatment. For a few subjects who were more than 15 percentiles below their baseline height curve at 2 years post-treatment, they either returned to baseline comparable height percentiles at 6 years post-treatment or a non-treatment related causative factor has been identified. The extent of available data is not sufficient to conclude that growth inhibition due to Pegasys exposure is always reversible.

Laboratory values
Decreases in haemoglobin, neutrophils and platelets may require dose reduction or permanent discontinuation from treatment (see Table 3 and Table 7). Most laboratory abnormalities noted during the clinical trial returned to baseline levels shortly after discontinuation of treatment.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

Overdoses involving between two injections on consecutive days (instead of weekly interval) up to daily injections for 1 week (i.e., 1260 micrograms/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 micrograms have been administered in renal cell carcinoma and chronic myelogenous leukaemia clinical trials, respectively. Dose limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia, consistent with interferon therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB11

Mechanism of action

The conjugation of PEG reagent (bis-monomethoxypolyethylene glycol) to interferon alfa-2a forms a pegylated interferon alfa-2a (Pegasys). Pegasys possesses the *in vitro* antiviral and antiproliferative activities that are characteristic of interferon alfa-2a.

Interferon alfa-2a is conjugated with bis-[monomethoxy polyethylene glycol] at a degree of substitution of one mole of polymer/mole of protein. The average molecular mass is approximately 60,000 of which the protein moiety constitutes approximately 20,000.

Pharmacodynamic effects

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received treatment with 180 micrograms Pegasys. The first phase of decline occurs 24 to 36 hours after the first dose of Pegasys and is followed by the second phase of decline which continues over the next 4 to 16 weeks in patients who achieve a sustained response. Ribavirin had no significant effect on the initial viral kinetics over the first 4 to 6 weeks in patients treated with the combination of ribavirin and pegylated interferon alfa-2a or interferon alfa.

Clinical efficacy and safety

Chronic hepatitis B

All clinical trials recruited patients with chronic hepatitis B who had active viral replication measured by HBV DNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. Study WV16240 recruited patients who were positive for HBeAg, while study WV16241 recruited patients who were negative for HBeAg and positive for anti-HBe. In both studies the treatment duration was 48 weeks, with 24 weeks of treatment-free follow-up. Both studies compared Pegasys plus placebo vs Pegasys plus lamivudine vs lamivudine alone. No HBV-HIV co-infected patients were included in these clinical trials.

Response rates at the end of follow-up for the two studies are presented in Table 11. In study WV16240, the primary efficacy endpoints were HBeAg seroconversion and HBV-DNA below 10^5 copies/ml. In study WV16241, the primary efficacy endpoints were ALT normalisation and HBV-DNA below 2×10^4 copies/ml. HBV-DNA was measured by the COBAS AMPLICOR™ HBV MONITOR Assay (limit of detection 200 copies/ml).

A total of 283/1351 (21%) of patients had advanced fibrosis or cirrhosis, 85/1351 (6%) had cirrhosis. There was no difference in response rate between these patients and those without advanced fibrosis or cirrhosis.

Table 11: Serological, virological and biochemical responses in chronic hepatitis B

	HBeAg positive Study WV16240			**HBeAg negative / anti-HBe positive Study WV16241**		
Response Parameter	**Pegasys** 180 mcg & **Placebo** (N=271)	**Pegasys** 180 mcg & **Lamivudine** 100 mg (N=271)	**Lamivudine** 100 mg (N=272)	**Pegasys** 180 mcg & **Placebo** (N=177)	**Pegasys** 180 mcg & **Lamivudine** 100 mg (N=179)	**Lamivudine** 100 mg (N=181)
HBeAg Sero-conversion	32% #	27%	19%	N/A	N/A	N/A
HBV DNA response *	32% #	34%	22%	43% #	44%	29%
ALT Normal-isation	41% #	39%	28%	59% #	60%	44%
HBsAg Sero-conversion	3% #	3%	0%	3%	2%	0%

* For HBeAg-positive patients: HBV DNA < 10^5 copies/ml
For HBeAg-negative/anti-HBe-positive patients: HBV DNA < 2×10^4 copies/ml

p-value (vs. lamivudine) $\leq$ 0.01 (stratified Cochran-Mantel-Haenszel test)

Histological response was similar across the three treatment groups in each study; however, patients showing a sustained response 24 weeks after the end of treatment were significantly more likely to also show histological improvement.

All patients who completed the phase III studies were eligible for entry into a long-term follow-up study (WV16866). Among patients from study WV16240, who received Pegasys monotherapy and entered the long-term follow-up study, the rate of sustained HBeAg seroconversion 12 months after the end of therapy was 48% (73/153). In patients receiving Pegasys monotherapy in study WV16241, the rate of HBV DNA response and ALT normalisation 12 months after end of treatment were 42% (41/97) and 59% (58/99), respectively.

Chronic hepatitis C

Predictability of response
Please refer to section 4.2, in Table 2.

Dose-response in monotherapy
In a direct comparison with 90 micrograms, the 180 micrograms-dose was associated with superior sustained virological response in patients with cirrhosis, but in a study in non-cirrhotic patients very similar results were obtained with doses of 135 micrograms and 180 micrograms.

Confirmatory clinical trials in adult treatment-naïve patients
All clinical trials recruited interferon-naïve patients with chronic hepatitis C confirmed by detectable levels of serum HCV RNA, elevated levels of ALT (with the exception of study NR16071) and a liver biopsy consistent with chronic hepatitis. Study NV15495 specifically recruited patients with a histological diagnosis of cirrhosis (about 80%) or transition to cirrhosis (about 20%). Only HIV-HCV co-infected patients were included in the study NR15961 (see Table 20). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl.
For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see Tables 12, 13, 14 and Table 20, respectively. Virological response was defined as undetectable HCV RNA as measured by the COBAS AMPLICOR™ HCV Test, version 2.0 (limit of detection 100 copies/ml equivalent to 50 International Units/ml) and sustained response as one negative sample approximately 6 months after end of therapy.

Table 12: Virological response in HCV patients

	Pegasys monotherapy				**Pegasys combination therapy**		
	non-cirrhotic and cirrhotic		**cirrhotic**		**non-cirrhotic and cirrhotic**		
	Study NV15496 + NV15497 + NV15801		**Study NV15495**		**Study NV15942**	**Study NV15801**	
	Pegasys 180 mcg (N=701) 48 weeks	**Interferon alfa-2a** 6 MIU/3 MIU & 3 MIU (N=478) 48 weeks	**Pegasys** 180 mcg (N=87) 48 weeks	**Interferon alfa-2a** 3 MIU (N=88) 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg (N=436) 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg (N=453) 48 weeks	**Interferon alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg (N=444) 48 weeks
Response at End of Treatment	55 - 69%	22 - 28%	44%	14%	68%	69%	52%
Overall Sustained Response	28 - 39%	11 - 19%	30%*	8%*	63%	54%**	45%**

* 95% CI for difference: 11% to 33% p-value (stratified Cochran-Mantel-Haenszel test) = 0.001
** 95% CI for difference: 3% to 16% p-value (stratified Cochran-Mantel-Haenszel test) = 0.003

The virological responses of HCV monoinfected patients treated with Pegasys and ribavirin combination therapy in relation to genotype and pre-treatment viral load and in relation to genotype, pre-treatment viral load and rapid virological response at week 4 are summarised in Table 13 and Table 14, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype, baseline viral load and virological response at week 4 (see Tables 1, 13 and 14).

The difference between treatment regimens was in general not influenced by presence/absence of cirrhosis; therefore treatment recommendations for genotype 1, 2 or 3 are independent of this baseline characteristic.

Table 13: Sustained virological response based on genotype and pre-treatment viral load after Pegasys combination therapy with ribavirin in HCV patients

	Study NV15942				Study NV15801	
	Pegasys 180 mcg & **Ribavirin** 800 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Interferon alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg 48 weeks
Genotype 1	29% (29/101)	42% (49/118)* 52% (37/71)	41% (102/250)*	52% (142/271)* 65% (55/85)	45% (134/298) 53% (61/115)	36% (103/285) 44% (41/94)
Low viral load	41% (21/51)	26% (12/47)	55% (33/60)	47% (87/186)	40% (73/182)	33% (62/189)
High viral load	16% (8/50)		36% (69/190)			
Genotype 2/3	84% (81/96)	81% (117/144)	79% (78/99)	80% (123/153)	71% (100/140)	61% (88/145)
Low viral load	85% (29/34)	83% (39/47)	88% (29/33)	77% (37/48)	76% (28/37)	65% (34/52)
High viral load	84% (52/62)	80% (78/97)	74% (49/66)	82% (86/105)	70% (72/103)	58% (54/93)
Genotype 4	(0/5)	(8/12)	(5/8)	(9/11)	(10/13)	(5/11)

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
*Pegasys 180 mcg & ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg & ribavirin 800 mg, 48 w:
Odds Ratio (95% CI) = 1.52 (1.07 to 2.17), P-value (stratified Cochran-Mantel-Haenszel test) = 0.020
*Pegasys 180 mcg & ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg & ribavirin 1000/1200 mg, 24 w:
Odds Ratio (95% CI) = 2.12 (1.30 to 3.46), P-value (stratified Cochran-Mantel-Haenszel test) = 0.002.

The possibility to consider shortening treatment duration to 24 weeks in genotype 1 and 4 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response at week 4 in studies NV15942 and ML17131 (see Table 14).

Table 14: Sustained virological response based on rapid viral response at week 4 for genotype 1 and 4 after Pegasys combination therapy with ribavirin in HCV patients

	Study NV15942		Study ML17131
	Pegasys 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks
Genotype 1 RVR	90% (28/31)	92% (47/51)	77% (59/77)
Low viral load	93% (25/27)	96% (26/27)	80% (52/65)
High viral load	75% (3/4)	88% (21/24)	58% (7/12)
Genotype 1 non RVR	24% (21/87)	43% (95/220)	- -
Low viral load	27% (12/44)	50% (31/62)	-
High viral load	21% (9/43)	41% (64/158)	
Genotype 4 RVR	(5/6)	(5/5)	92% (22/24)
Genotype 4 non RVR	(3/6)	(4/6)	-

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24

Although limited, data indicated that shortening treatment to 24 weeks might be associated with a higher risk of relapse (see Table 15).

Table 15: Relapse of virological response at the end of treatment for rapid virological response population

	Study NV15942		Study NV15801
	Pegasys 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks
Genotype 1 RVR	6.7% (2/30)	4.3% (2/47)	0% (0/24)
Low viral load	3.8% (1/26)	0% (0/25)	0% (0/17)
High viral load	25% (1/4)	9.1% (2/22)	0% (0/7)
Genotype 4 RVR	(0/5)	(0/5)	0% (0/4)

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on a sustained virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 16).

In study NV17317 in patients infected with viral genotype 2 or 3, all patients received Pegasys 180 mcg sc qw and a ribavirin dose of 800 mg and were randomised to treatment for either 16 or 24 weeks. Overall treatment for 16 weeks resulted in lower sustained viral response (65%) than treatment for 24 weeks (76%) ($p < 0.0001$).

The sustained viral response achieved with 16 weeks of treatment and with 24 weeks of treatment was also examined in a retrospective subgroup analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline (see Table 16).

Table 16: Sustained virological response overall and based on rapid viral response by week 4 for genotype 2 or 3 after Pegasys combination therapy with ribavirin in HCV patients

Study NV17317				
	Pegasys 180 mcg & **Ribavirin** 800 mg 16 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	Treatment difference [95%CI]	p value
Genotype 2 or 3	65% (443/679)	76% (478/630)	-10.6% [-15.5% ; -0.06%]	P<0.0001
Genotype 2 or 3 RVR	82% (378/461)	90% (370/410)	-8.2% [-12.8% ; -3.7%]	P=0.0006
Low viral load	89% (147/166)	94% (141/150)	-5.4% [-12% ; 0.9%]	P=0.11
High viral load	78% (231/295)	88% (229/260)	-9.7% [-15.9% ;-3.6%]	P=0.002

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4

It is presently not clear whether a higher dose of ribavirin (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The data indicated that shortening treatment to 16 weeks is associated with a higher risk of relapse (see Table 17).

Table 17: Relapse of virological response after the end of treatment in genotype 2 or 3 patients with a rapid viral response

Study NV17317				
	Pegasys 180 mcg & **Ribavirin** 800 mg 16 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	Treatment difference [95%CI]	p value
Genotype 2 or 3 RVR	15% (67/439)	6% (23/386)	9.3% [5.2% ; 13.6%]	P<0.0001
Low viral load	6% (10/155)	1% (2/141)	5% [0.6% ; 10.3%]	P=0.04
High viral load	20% (57/284)	9% (21/245)	11.5% [5.6% ; 17.4%]	P=0.0002

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4

Superior efficacy of Pegasys compared to interferon alfa-2a was demonstrated also in terms of histological response, including patients with cirrhosis and/or HIV-HCV co-infection.

Adult chronic hepatitis C prior treatment non-responder patients
In study MV17150, patients who were non-responders to previous therapy with pegylated interferon alfa-2b plus ribavirin were randomised to four different treatments:

- Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 60 weeks
- Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 36 weeks
- Pegasys 180 mcg/week for 72 weeks
- Pegasys 180 mcg/week for 48 weeks

All patients received ribavirin (1000 or 1200 mg/day) in combination with Pegasys. All treatment arms had 24 week treatment-free follow-up.

Multiple regression and pooled group analyses evaluating the influence of treatment duration and use of induction dosing clearly identified treatment duration for 72 weeks as the primary driver for achieving a sustained virological response. Differences in sustained virological response (SVR) based on treatment duration, demographics and best responses to previous treatment are displayed in Table 18.

Table 18: Week 12 virological response (VR) and sustained virological response (SVR) in patients with virological response at week 12 after treatment with Pegasys and ribavirin combination therapy in nonresponders to peginterferon alfa-2b plus ribavirin

Study MV17150			
	Pegasys 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 72 or 48 Weeks (N = 942) **Pts with VR at Wk 12** [a] **(N = 876)**	**Pegasys** 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 72 Weeks (N = 473) **SVR in Pts with VR at Wk 12** [b] **(N = 100)**	**Pegasys** 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 48 Weeks (N = 469) **SVR in Pts with VR at Wk 12** [b] **(N = 57)**
Overall	18% (157/876)	57% (57/100)	35% (20/57)
Low viral load	35% (56/159)	63% (22/35)	38% (8/21)
High viral load	14% (97/686)	54% (34/63)	32% (11/34)
Genotype 1/4	17% (140/846)	55% (52/94)	35% (16/46)
Low viral load	35% (54/154)	63% (22/35)	37% (7/19)
High viral load	13% (84/663)	52% (30/58)	35% (9/26)
Genotype 2/3	58% (15/26)	(4/5)	(3/10)
Low viral load	(2/5)	—	(1/2)
High viral load	(11/19)	(3/4)	(1/7)
Cirrhosis Status			
Cirrhosis	8% (19/239)	(6/13)	(3/6)
Noncirrhosis	22% (137/633)	59% (51/87)	34% (17/50)
Best Response during Previous Treatment			
$\geq 2\log_{10}$ decline in HCV RNA	28% (34/121)	68% (15/22)	(6/12)
$<2\log_{10}$ decline in HCV RNA	12% (39/323)	64% (16/25)	(5/14)
Missing best previous response	19% (84/432)	49% (26/53)	29% (9/31)

High viral load = > 800,000 IU/ml, low viral load = ≤ 800,000 IU/ml.

[a] Patients who achieved viral suppression (undetectable HCV RNA, < 50 IU/ml) at week 12 were considered to have a virological response at week 12. Patients missing HCV RNA results at week 12 have been excluded from the analysis.

[b] Patients who achieved viral suppression at week 12 but were missing HCV RNA results at the end of follow-up were considered to be non-responders.

In the HALT-C study, patients with chronic hepatitis C and advanced fibrosis or cirrhosis who were non-responders to previous treatment with interferon alfa or pegylated interferon alfa monotherapy or in combination therapy with ribavirin were treated with Pegasys 180 mcg/week and ribavirin 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on Pegasys plus ribavirin combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. The probability for sustained virological response varied depending upon the previous treatment regimen; see Table 19.

Table 19: Sustained virological response in HALT-C by previous treatment regimen in non-responder population

Previous Treatment	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks
Interferon	27% (70/255)
Pegylated interferon	34% (13/38)
Interferon plus ribavirin	13% (90/692)
Pegylated interferon plus ribavirin	11% (7/61)

HIV-HCV co-infected patients
The virological responses of patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and pre-treatment viral load for HIV-HCV co-infected patients are summarised below in Table 20.

Table 20: Sustained virological response based on genotype and pre-treatment viral load after Pegasys combination therapy with ribavirin in HIV-HCV co-infected patients

Study NR15961			
	Interferon alfa-2a 3 MIU & **Ribavirin 800 mg** 48 weeks	**Pegasys** 180 mcg & **Placebo** 48 weeks	**Pegasys** 180 mcg & **Ribavirin 800 mg** 48 weeks
All patients	12% (33/285)*	20% (58/286)*	40% (116/289)*
Genotype 1 Low viral load High viral load	7% (12/171) 19% (8/42) 3% (4/129)	14% (24/175) 38% (17/45) 5% (7/130)	29% (51/176) 61% (28/46) 18% (23/130)
Genotype 2-3 Low viral load High viral load	20% (18/89) 27% (8/30) 17% (10/59)	36% (32/90) 38% (9/24) 35% (23/66)	62% (59/95) 61% (17/28) 63% (42/67)

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
* Pegasys 180 mcg & ribavirin 800 mg vs. Interferon alfa-2a 3 MIU & ribavirin 800 mg:
Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001
* Pegasys 180 mcg & ribavirin 800 mg vs. Pegasys 180 mcg:
Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001
* Interferon alfa-2a 3 MIU & ribavirin 800 mg vs. Pegasys 180 mcg:
Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared treatment using Pegasys 180 mcg/week and either ribavirin 800 mg or 1000 mg (<75 kg)/1200 mg (≥75 kg) daily for 48 weeks. The study was not powered for efficacy considerations. The safety profiles in both ribavirin groups were consistent with the known safety profile of Pegasys plus ribavirin combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose ribavirin arm.

HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomised to receive Pegasys 180 micrograms/week and ribavirin 800 milligrams/day for either 24 or 48 weeks followed by a 24 week treatment free follow-up period or no treatment for 72 weeks. The SVRs reported in the treatment arms of this study were similar to the corresponding treatment arms from study NV15942.

Paediatric population
In the investigator sponsored CHIPS study (Chronic Hepatitis C International Paediatric Study), 65 children and adolescents (6-18 years) with chronic HCV infection were treated with Pegasys 100 mcg/m^2 sc once weekly and ribavirin 15 mg/kg/day for 24 weeks (genotypes 2 and 3) or 48 weeks (all other genotypes). Preliminary and limited safety data demonstrated no obvious departure from the known safety profile of the combination in adults with chronic HCV infection, but, importantly, the potential impact on growth has not been reported. Efficacy results were similar to those reported in adults.

In the NV17424 (PEDS-C) study, previously untreated paediatric patients 5 to 17 years of age (55% <12 years old) with compensated chronic hepatitis C and detectable HCV RNA were treated with Pegasys 180 mcg x BSA/1.73 m^2 once weekly for 48 weeks with or without ribavirin 15 mg/kg/day. All patients were followed for 24 weeks post-treatment. A total of 55 patients received initial combination treatment of Pegasys plus ribavirin, of whom 51% were female, 82% were Caucasian, and 82% were infected with HCV genotype 1. The study efficacy results for these patients are summarised in Table 21.

Table 21: Sustained virological response in the NV17424 study

	Pegasys 180 mcg x BSA/1.73 m² + Ribavirin 15 mg/kg (N=55)*
All HCV genotypes**	29 (53%)
HCV genotype 1	21/45 (47%)
HCV genotype 2 and 3	8/10 (80%)

*Results indicate undetectable HCV-RNA defined as HCV RNA less than 50 IU/ml at 24 weeks post-treatment using the AMPLICOR HCV test v2.
**Scheduled treatment duration was 48 weeks regardless of the genotype

5.2 Pharmacokinetic properties

Absorption
Following a single subcutaneous injection of Pegasys 180 micrograms in healthy subjects, serum concentrations of peginterferon alfa-2a are measurable within 3 to 6 hours. Within 24 hours, about 80% of the peak serum concentration is reached. The absorption of Pegasys is sustained with peak serum concentrations reached 72 to 96 hours after dosing. The absolute bioavailability of Pegasys is 84% and is similar to that seen with interferon alfa-2a.

Distribution
Peginterferon alfa-2a is found predominantly in the bloodstream and extracellular fluid as seen by the volume of distribution at steady-state (V_d) of 6 to 14 litres in humans after intravenous administration. From mass balance, tissue distribution and whole body autoradioluminography studies performed in rats, peginterferon alfa-2a is distributed to the liver, kidney and bone marrow in addition to being highly concentrated in the blood.

Biotransformation
The metabolism of Pegasys is not fully characterised; however studies in rats indicate that the kidney is a major organ for excretion of radiolabelled material.

Elimination
In humans, the systemic clearance of peginterferon alfa-2a is about 100-fold lower than that of the native interferon alfa-2a. After intravenous administration, the terminal half-life of peginterferon alfa-2a in healthy subjects is approximately 60 to 80 hours compared to values of 3-4 hours for standard interferon. The terminal half-life after subcutaneous administration in patients is longer with a mean value of 160 hours (84 to 353 hours). The terminal half-life may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

Linearity/non-linearity
Dose-proportional increases in exposure of Pegasys are seen in healthy subjects and in patients with chronic hepatitis B or C after once-weekly dosing.

In chronic hepatitis B or C patients, peginterferon alfa-2a serum concentrations accumulate 2 to 3 fold after 6 to 8 weeks of once weekly dosing compared to single dose values. There is no further accumulation after 8 weeks of once weekly dosing. The peak to trough ratio after 48 weeks of treatment is about 1.5 to 2. Peginterferon alfa-2a serum concentrations are sustained throughout one full week (168 hours).

Patients with renal impairment
A clinical trial evaluated 50 CHC patients with either moderate (creatinine clearance 30 to 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment, or with end stage renal disease (ESRD) requiring chronic hemodialysis (HD). Patients with moderate renal impairment receiving

Pegasys 180 mcg once weekly exhibited similar peginterferon alfa-2a plasma exposures compared to patients with normal renal function. Patients with severe renal impairment receiving Pegasys 180 mcg once weekly showed a 60% higher peginterferon alfa-2a exposure than patients with normal renal function, therefore a reduced dose of Pegasys 135 mcg once weekly is recommended in patients with severe renal impairment. In 13 patients with ESRD requiring chronic HD, administration of Pegasys 135 mcg once weekly resulted in 34% lower peginterferon alfa-2a exposure than in patients with normal renal function. However, several independent studies have demonstrated the 135mcg dose to be safe, efficacious and well tolerated, in patients with ESRD.(see section 4.2).

Gender
The pharmacokinetics of Pegasys after single subcutaneous injections was comparable between male and female healthy subjects.

Paediatric population
In a population pharmacokinetic study (NR16141), 14 children 2 to 8 years of age with CHC received Pegasys monotherapy at a dose of: 180 mcg x BSA of the child/1.73 m^2. The PK model developed from this study shows a linear influence of BSA on the apparent clearance of the drug over the age range studied. Thus, the lower the BSA of the child, the lower the clearance of the drug and the higher the resultant exposure. The mean exposure (AUC) during the dosing interval is predicted to be 25% to 70% higher than that observed in adults receiving 180 mcg fixed dosing.

Elderly
In subjects older than 62 years, the absorption of Pegasys after a single subcutaneous injection of 180 micrograms was delayed but still sustained compared to young healthy subjects (t_{max} of 115 hours vs. 82 hours, older than 62 years vs. younger, respectively). The AUC was slightly increased (1663 vs. 1295 ng·h/ml) but peak concentrations (9.1 vs. 10.3 ng/ml) were similar in subjects older than 62 years. Based on drug exposure, pharmacodynamic response and tolerability, a lower dose of Pegasys is not needed in the geriatric patient (see section 4.2).

Hepatic impairment
The pharmacokinetics of Pegasys were similar between healthy subjects and patients with hepatitis B or C. Comparable exposure and pharmacokinetic profiles were seen in cirrhotic (Child-Pugh Grade A) and non-cirrhotic patients.

Site of administration
Subcutaneous administration of Pegasys should be limited to the abdomen and thigh, as the extent of absorption based on AUC was about 20% to 30% higher upon injection in the abdomen and thigh. Exposure to Pegasys was decreased in studies following administration of Pegasys in the arm compared to administration in the abdomen and thigh.

5.3 Preclinical safety data

The non-clinical toxicity studies conducted with Pegasys were limited due to species specificity of interferons. Acute and chronic toxicity studies have been carried out in cynomolgus monkeys, and the findings observed in peginterferon dosed animals were similar in nature to those produced by interferon alfa-2a.

Reproductive toxicity studies have not been performed with Pegasys. As with other alfa interferons, prolongation of the menstrual cycle was observed following administration of peginterferon alfa-2a to female monkeys. Treatment with interferon alfa-2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys. Although no teratogenic effects were seen in the offspring delivered at term, adverse effects in humans cannot be excluded.

Pegasys plus ribavirin
When used in combination with ribavirin, Pegasys did not cause any effects in monkeys not previously seen with either active substance alone. The major treatment-related change was reversible mild to

moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Polysorbate 80
Benzyl alcohol
Sodium acetate
Acetic acid
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

Pegasys 90 micrograms solution for injection in pre-filled syringe
3 years.

Pegasys 135 micrograms solution for injection in pre-filled syringe
4 years

Pegasys 180 micrograms solution for injection in pre-filled syringe
4 years

6.4 Special precautions for storage

Store in a refrigerator (2°C-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 (siliconised Type I glass) with a plunger stopper and tip cap (butyl rubber laminated on the product facing side with fluororesin) with a needle.

Pegasys 90 micrograms solution for injection in pre-filled syringe
The syringe is labeled with graduations corresponding to doses of 90 mcg, 65 mcg, 45 mcg, 30 mcg, 20 mcg and 10 mcg. Available in packs of 1 pre-filled syringe.

Pegasys 135 micrograms solution for injection in pre-filled syringe
The syringe is labeled with graduations corresponding to doses of 135 mcg, 90 mcg and 45 mcg. Available in packs of 1, 4 or a multipack of 12 (2 packs of 6) pre-filled syringes. Not all pack-sizes may be marketed.

Pegasys 180 micrograms solution for injection in pre-filled syringe
The syringe is labeled with graduations corresponding to doses of 180 mcg, 135 mcg and 90 mcg. Available in packs of 1, 4 or a multipack of 12 (2 packs of 6) pre-filled syringes. Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

The solution for injection is for single use only. It should be inspected visually for particulate matter and discoloration before administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

Pegasys 90 micrograms solution for injection in pre-filled syringe
EU/1/02/221/017

Pegasys 135 micrograms solution for injection in pre-filled syringe
EU/1/02/221/005
EU/1/02/221/006
EU/1/02/221/009

Pegasys 180 micrograms solution for injection in pre-filled syringe
EU/1/02/221/007
EU/1/02/221/008
EU/1/02/221/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2002
Date of latest renewal: 20 June 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled pen
Pegasys 180 micrograms solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pegasys 135 micrograms solution for injection in pre-filled pen
Each pre-filled pen of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a*.

Pegasys 180 micrograms solution for injection in pre-filled pen
Each pre-filled pen of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a*.

The strength indicates the quantity of the interferon alfa-2a moiety of peginterferon alfa-2a without consideration of the pegylation.

*The active substance, peginterferon alfa-2a, is a covalent conjugate of the protein interferon alfa-2a produced by recombinant DNA technology in *Escherichia coli* with bis-[monomethoxy polyethylene glycol].

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1.

Excipient with known effect: Benzyl alcohol (10 mg/ 1 ml)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is clear and colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic hepatitis B

Pegasys is indicated for the treatment of hepatitis B envelope antigen (HBeAg)-positive or HBeAg-negative-chronic hepatitis B (CHB) in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis (see sections 4.4 and 5.1).

Chronic hepatitis C

Adult patients

Pegasys is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC) in patients with compensated liver disease (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.2 and 5.1.

Paediatric patients 5 years of age and older:
Pegasys in combination with ribavirin is indicated for the treatment of chronic hepatitis C in treatment-naïve children and adolescents 5 years of age and older who are positive for serum HCV-RNA.

When deciding to initiate treatment in childhood , it is important to consider growth inhibition induced by combination therapy. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

4.2 Posology and method of administration

Treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis B or C.

Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Pegasys.

Monotherapy for hepatitis C should only be considered in cases of contraindication to other medicinal products.

Posology

Chronic hepatitis B – adult patients

The recommended dosage and duration of Pegasys for both HBeAg-positive and HBeAg-negative chronic hepatitis B is 180 micrograms once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

Chronic hepatitis C – treatment-naïve adult patients

The recommended dose for Pegasys is 180 micrograms once weekly by subcutaneous administration in the abdomen or thigh given in combination with oral ribavirin or as monotherapy.

The dose of ribavirin to be used in combination with Pegasys is given in Table 1.
The ribavirin dose should be administered with food.

Duration of treatment –dual therapy with Pegasys and ribavirin

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 regardless of pre-treatment viral load should receive 48 weeks of therapy.
Treatment for 24 weeks may be considered in patients infected with
- genotype 1 with low viral load (LVL) (≤ 800,000 IU/ml) at baseline or
- genotype 4

who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1). In these patients, tolerability to combination therapy and additional prognostic factors such as degree of fibrosis should be taken into account when deciding on treatment duration. Shortening the treatment duration in patients with genotype 1 and high viral load (HVL) (>800, 000 IU/ml) at baseline who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24 should be considered with even more caution since the limited data available suggest that this may significantly negatively impact the sustained virologic response.

Patients infected with HCV genotype 2 or 3 who have detectable HCV RNA at week 4, regardless of pre-treatment viral load should receive 24 weeks of therapy. Treatment for only 16 weeks may be considered in selected patients infected with genotype 2 or 3 with LVL (≤ 800,000 IU/ml) at baseline who become HCV negative by week 4 of treatment and remains HCV negative by week 16. Overall

16 weeks of treatment may be associated with a lower chance of response and is associated with a higher risk of relapse than a 24 week treatment duration (see section 5.1). In these patients, tolerability to combination therapy and the presence of additional clinical or prognostic factors such as degree of fibrosis should be taken into account when considering deviations from standard 24 weeks treatment duration. Shortening the treatment duration in patients infected with genotype 2 or 3 with HVL (> 800,000 IU/ml) at baseline who become HCV negative by week 4 should be considered with more caution as this may significantly negatively impact the sustained virological response (see Table 1).

Available data for patients infected with genotype 5 or 6 are limited; therefore combination treatment with 1,000/1,200 mg of ribavirin for 48 weeks is recommended.

Table 1: Dosing recommendations for combination therapy for HCV patients

Genotype	Pegasys dose	Ribavirin dose	Duration
Genotype 1 LVL with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 4 with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 2 or 3 without RVR**	180 micrograms	800 mg	24 weeks
Genotype 2 or 3 LVL with RVR**	180 micrograms	800 mg[(a)]	16 weeks[(a)] or 24 weeks
Genotype 2 or 3 HVL with RVR**	180 micrograms	800 mg	24 weeks

*RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24;
**RVR = rapid viral response (HCV RNA negative) by week 4
LVL = ≤ 800,000 IU/ml; HVL = > 800,000 IU/ml
[(a)] It is presently not clear whether a higher dose of ribavirin (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The ultimate clinical impact of a shortened initial treatment of 16 weeks instead of 24 weeks is unknown, taking into account the need for re-treating non-responding and relapsing patients.

The recommended duration of Pegasys monotherapy is 48 weeks.

Chronic hepatitis C – treatment-experienced adult patients

The recommended dose of Pegasys in combination with ribavirin is 180 mcg once weekly by subcutaneous administration. For patients <75 kg and ≥75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, and regardless of genotype, should be administered.
Patients who have detectable virus at week 12 should stop therapy. The recommended total duration of therapy is 48 weeks. If patients infected with virus genotype 1, not responding to prior treatment with peginterferon and ribavirin are considered for treatment, the recommended total duration of therapy is 72 weeks (see section 5.1).

HIV-HCV co-infected adult patients

The recommended dosage for Pegasys, alone or in combination with ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks. For patients infected with HCV genotype 1 <75 kg and ≥75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, should be administered. Patients infected with HCV genotypes other than genotype 1 should receive 800 mg daily of ribavirin. A duration of therapy less than 48 weeks has not been adequately studied.

Duration of therapy when Pegasys is used in combination with other medicinal products

Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Pegasys.

Predictability of response and non-response with Pegasys and ribavirin dual therapy – treatment-naïve patients

Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see Tables 2 and 12).

Table 2: Predictive value of week 12 virological response at the recommended dosing regimen while on Pegasys combination therapy

Genotype	**Negative**			**Positive**		
	No response by week 12	No sustained response	Predictive Value	Response by week 12	Sustained response	Predictive Value
Genotype 1 (N= 569)	102	97	**95%** (97/102)	467	271	**58%** (271/467)
Genotype 2 and 3 (N=96)	3	3	**100%** (3/3)	93	81	**87%** (81/93)

The negative predictive value for sustained response in patients treated with Pegasys in monotherapy was 98%.
A similar negative predictive value has been observed in HIV-HCV co-infected patients treated with Pegasys monotherapy or in combination with ribavirin (100% (130/130) or 98% (83/85), respectively). Positive predictive values of 45% (50/110) and 70% (59/84) were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Predictability of response and non-response with Pegasys and ribavirin dual therapy – treatment-experienced patients

In non-responder patients re-treated for 48 or 72 weeks, viral suppression at week 12 (undetectable HCV RNA defined as <50 IU/ml) has been shown to be predictive for sustained virological response. The probabilities of not achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was not achieved at week 12 were 96% (363 of 380) and 96% (324 of 339), respectively. The probabilities of achieving a sustained virological response with 48 or 72 weeks of treatment if viral suppression was achieved at week 12 were 35% (20 of 57) and 57% (57 of 100), respectively.

Dose adjustment for adverse reactions in adult patients

General
Where dose adjustment is required for moderate to severe adverse reactions (clinical and/or laboratory) initial dose reduction to 135 micrograms is generally adequate for adult patients. In some cases, dose reduction to 90 micrograms or 45 micrograms is necessary. Dose increases to or towards the original dose may be considered when the adverse reaction abates (see sections 4.4 and section 4.8).

Haematological (see also Table 3)
For adults, dose reduction is recommended if the neutrophil count is < 750/mm^3. For patients with Absolute Neutrophil Count (ANC) < 500/mm^3 treatment should be suspended until ANC values return to > 1000/mm^3. Therapy should initially be re-instituted at 90 micrograms Pegasys and the neutrophil count monitored. Guidance for dose reduction based on ANC levels for paediatric patients is provided in Table 7.

Dose reduction to 90 micrograms is recommended if the platelet count is < 50,000/mm^3. Cessation of therapy is recommended when platelet count decreases to levels < 25,000/mm^3.

Specific recommendations for management of treatment-emergent anaemia in adults are as follows: ribavirin should be reduced to 600 milligrams/day (200 milligrams in the morning and 400 milligrams in the evening) if either of the following apply: (1) a patient without significant cardiovascular disease experiences a fall in haemoglobin to < 10 g/dl and ≥ 8.5 g/dl, or (2) a patient with stable cardiovascular disease experiences a fall in haemoglobin by ≥ 2 g/dl during any 4 weeks of treatment. A return to original dosing is not recommended. Ribavirin should be discontinued if either of the following applies: (1) a patient without significant cardiovascular disease experiences a fall in haemoglobin confirmed to < 8.5 g/dl; (2) a patient with stable cardiovascular disease maintains a haemoglobin value < 12 g/dl despite 4 weeks on a reduced dose. If the abnormality is reversed, ribavirin may be restarted at 600 milligrams daily, and further increased to 800 milligrams daily at the discretion of the treating physician. A return to original dosing is not recommended.

Table 3: Dose adjustment for adverse reaction (for further guidance see also text above)

	Reduce ribavirin to 600 mg	Withhold ribavirin	Reduce Pegasys to 135/90/45 micrograms	Withhold Pegasys	Discontinue combination
Absolute Neutrophil Count			< 750/mm^3	< 500/mm^3	
Platelet Count			< 50,000/mm^3 > 25,000/mm^3		< 25,000/mm^3
Haemoglobin - no cardiac disease	< 10 g/dl, and ≥ 8.5 g/dl	< 8.5 g/dl			
Haemoglobin - stable cardiac disease	decrease ≥ 2 g/dl during any 4 weeks	< 12 g/dl despite 4 weeks at reduced dose			

In case of intolerance to ribavirin, Pegasys monotherapy should be continued.

Liver function
Fluctuations in abnormalities of liver function tests are common in patients with chronic hepatitis C. Increases in ALT levels above baseline (BL) have been observed in patients treated with Pegasys, including patients with a virological response.
In chronic hepatitis C clinical trials with adult patients, isolated increases in ALT (≥ 10x ULN, or ≥ 2x BL for patients with a BL ALT ≥ 10x ULN) which resolved without dose-modification were observed in 8 of 451 patients treated with combination therapy. If ALT increase is progressive or persistent, the dose should be reduced initially to 135 micrograms. When increases in ALT levels are progressive despite dose reduction, or are accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see section 4.4). Guidance for dose reduction based on ALT levels for paediatric patients is provided in Table 7.

For chronic hepatitis B patients, transient flares of ALT levels sometimes exceeding 10 times the upper limit of normal are not uncommon, and may reflect immune clearance. Treatment should normally not be initiated if ALT is >10 times the upper limit of normal. Consideration should be given to continuing treatment with more frequent monitoring of liver function during ALT flares. If the Pegasys dose is reduced or withheld, therapy can be restored once the flare is subsiding (see section 4.4).

Special populations

Elderly
Adjustments in the recommended dosage of 180 micrograms once weekly are not necessary when instituting Pegasys therapy in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is required for adult patients with mild or moderate renal impairment. A reduced dose of 135 mcg once weekly is recommended in adult patients with severe renal impairment or end stage renal disease (see section 5.2). Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of Pegasys during the course of therapy should be made in the event of adverse reactions.

Hepatic impairment
In patients with compensated cirrhosis (e.g., Child-Pugh A), Pegasys has been shown to be effective and safe. Pegasys has not been evaluated in patients with decompensated cirrhosis (e.g., Child-Pugh B or C or bleeding oesophageal varices) (see section 4.3).

The Child-Pugh classification divides patients into groups A, B, and C, or "Mild", "Moderate" and "Severe" corresponding to scores of 5-6, 7-9 and 10-15, respectively.

Modified Assessment

Assessment	Degree of abnormality	Score
Encephalopathy	None Grade 1-2 Grade 3-4*	1 2 3
Ascites	Absent Slight Moderate	1 2 3
S-Bilirubin (mg/dl) SI unit = μmol/l)	<2 2.0-3 >3 <34 34-51 >51	1 2 3 1 2 3
S-Albumin (g/dl)	>3.5 3.5-2.8 <2.8	1 2 3
INR	<1.7 1.7-2.3 >2.3	1 2 3

*Grading according to Trey, Burns and Saunders (1966)

Paediatric population

Pegasys is contraindicated in neonates and young children up to 3 years old due to the excipient benzyl alcohol (see sections 4.3 and 4.4).

For children and adolescents aged 5 to 17 years with chronic hepatitis C, and having a Body Surface Area (BSA) greater than 0.7 m^2, the recommended doses for Pegasys and ribavirin are provided in Table 4 and Table 5. It is recommended that Pegasys pre-filled syringes be used for paediatric patients. The Pegasys pre-filled pens do not allow for appropriate adjustment of dosing in these patients. Patients who initiate treatment prior to their 18^{th} birthday should maintain paediatric dosing through the completion of therapy.

Pegasys should not be used in children with a Body Surface Area (BSA) less than 0.71 as there is no available data for this subpopulation.

To calculate BSA, it is recommended to use Mosteller's equation:

$$BSA\ (m^2) = \sqrt{\left(\frac{Height\ (cm) \times Weight\ (kg)}{3600}\right)}$$

Duration of treatment
The duration of treatment with Pegasys in combination with ribavirin in paediatric patients with chronic hepatitis C depends on viral genotype. Patients infected with viral genotypes 2 or 3 should receive 24 weeks of treatment, while patients infected with any other genotype should receive 48 weeks of therapy.

Patients who still have detectable levels of HCV-RNA despite an initial 24 weeks of therapy, should discontinue therapy, as it is unlikely they will be able to achieve a sustained virological response with continued therapy.

Table 4: Pegasys dosing recommendations for paediatric patients aged 5 to 17 years

Body Surface Area (BSA) range (m^2)	Weekly dose (mcg)
0.71-0.74	65
0.75-1.08	90
1.09-1.51	135
>1.51	180

For children and adolescents aged 5 to 17 years with chronic hepatitis C, the recommended dose of ribavirin is based on the patient's body weight, with a target dose of 15 mg/kg/day, divided in two daily doses. For children and adolescents 23 kg or greater, a dosing schedule using 200 mg ribavirin tablets is provided in Table 5. Patients and caregivers must not attempt to break the 200 mg tablets.

Table 5: Ribavirin dosing recommendations for paediatric patients aged 5 to 17 years

Body weight kg (lbs)	Ribavirin daily dose (Approx. 15 mg/kg/day)	Ribavirin number of tablets
23 – 33 (51-73)	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
34 – 46 (75-101)	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
47 – 59 (103-131)	800 mg/day	2 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
60 – 74 (132-163)	1000 mg/day	2 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.
≥75 (>165)	1200 mg/day	3 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.

Dose adjustment for adverse reactions in paediatric patients

For paediatric patients, based on toxicities (see Table 6), up to three levels of dose modification can be made before dose interruption or discontinuation is considered.

Table 6: Pegasys dose modification recommendations in paediatric patients

Starting dose (mcg)	**1 level reduction (mcg)**	**2 level reduction (mcg)**	**3 level reduction (mcg)**
65	45	30	20
90	65	45	20
135	90	65	30
180	135	90	45

If toxicities occur which may be related to Pegasys and/or ribavirin administration, the dose of one or both medicinal products can be reduced. Additionally, ribavirin or Pegasys plus ribavirin combination therapy can be discontinued. It is important to note that ribavirin should never be given as monotherapy. Recommendations for dose modifications for toxicities known to have an association with Pegasys administration that are specific for the paediatric population are presented in Table 7. Unless otherwise noted, the management of all other toxicities should follow the adult recommendations.

Table 7: Pegasys dose modification recommendations for toxicities in paediatric patients

Toxicity	Pegasys dose modification
Neutropenia	750-999 cells/mm^3: Week 1-2 - immediate 1 level adjustment; Week 3-48: no modification. 500-749 cells/mm^3: Week 1-2 - interrupt dosing until >750 cells/mm^3 then resume dose with a 1 level adjustment, assess weekly for the next 3 weeks to verify ANC >750 cells/mm^3; Week 3-48 - immediate 1 level adjustment. 250-499 cells/mm^3: Week 1-2 - interrupt dosing until >750 cells/mm^3 then resume dose with a 2 level adjustment; Week 3-48 - interrupt dosing until >750 cells/mm^3 then resume dose with a 1 level adjustment. < 250 cells/mm^3 (or febrile neutropenia) discontinue treatment.
Increased alanine transaminase (ALT)	For persistent or increasing elevations ≥5 but <10 x ULN, reduce dose with a 1 level adjustment and monitor weekly ALT level to ensure it is stable or decreasing For persistent ALT values ≥10 x ULN discontinue treatment.

In paediatric patients, ribavirin treatment-associated toxicities, such as treatment-emergent anaemia, will be managed by reduction of the full dose. The dose reduction levels are provided in Table 8.

Table 8: Ribavirin dose modification recommendations in paediatric patients

Full dose (Approx. 15 mg/kg/day)	**One step dose modification** (Approx. 7.5 mg/kg/day)	**Ribavirin number of tablets**
400 mg/day	200 mg/day	1 x 200 mg tablets A.M.
600 mg/day	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
800 mg/day	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
1000 mg/day	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
1200 mg/day	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.

There is limited experience with Pegasys in treating paediatric patients with HCV aged 3 to 5 years, or who have failed to be adequately treated previously. There are no data in paediatric patients coinfected with HCV/HIV or with renal impairment.

Method of administration

Pegasys is administered subcutaneously in the abdomen or thigh. Exposure to Pegasys was decreased in studies following administration of Pegasys in the arm (see section 5.2).

Pegasys is designed for administration by the patient or carer. Each pen should be used by one person only and is for single use.

Appropriate training is recommended for non-healthcare professionals administering this medicinal product. The “Instructions for the User”, provided in the carton, must be followed carefully by the patient.

4.3 Contraindications

- Hypersensitivity to the active substance, to alfa interferons, or to any of the excipients listed in section 6.1
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4)
- HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6, except if only due to indirect hyperbilirubinemia caused by medicinal products such as atazanavir and indinavir
- Combination with telbivudine (see section 4.5).
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol (see section 4.4 for benzyl alcohol)
- In paediatric patients, the presence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Pegasys therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alfa interferons. All patients should be closely monitored for any signs or symptoms of psychiatric disorders. If symptoms of psychiatric disorders 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, it is recommended that treatment with Pegasys be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions: If treatment with Pegasys is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
The use of Pegasys in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).

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 alfa interferon. If treatment with alfa 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.

Growth and development (children and adolescents): During the course of Pegasys plus ribavirin therapy lasting up to 48 weeks in patients aged 5 to 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1).

The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials on a case by case basis (see sections 4.8 and 5.1).

- It is important to consider that the combination therapy induced a growth inhibition during treatment, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

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

Laboratory tests prior to and during therapy

Prior to beginning Pegasys 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 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 (including glucose monitoring).

In clinical trials, Pegasys treatment was associated with decreases in both total white blood cell (WBC) count and absolute neutrophil count (ANC), usually starting within the first 2 weeks of treatment (see section 4.8). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see section 4.2), reached normal values by 8 weeks in the majority of patients and returned to baseline in all patients after about 16 weeks.

Pegasys treatment has been associated with decreases in platelet count, which returned to pre-treatment levels during the post-treatment observation period (see section 4.8). In some cases, dose modification may be necessary (see section 4.2).

The occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 15% of chronic hepatitis C patients in clinical trials on the combined treatment of Pegasys with ribavirin. The frequency depends on the treatment duration and the dose of ribavirin (see section 4.8,). The risk of developing anaemia is higher in the female population.

Caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a peginterferon and ribavirin concomitantly with azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon re-introduction of either treatment alone (see section 4.5).

The use of Pegasys 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 haematological adverse reactions. 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 alfa interferons, including Pegasys. Prior to initiation of Pegasys therapy, TSH and T4 levels should be evaluated. Pegasys treatment may be initiated or continued if TSH levels can be maintained in the normal range by pharmaceutical means. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see section 4.8). Hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Pegasys (see section 4.8). Patients with these conditions who cannot be effectively controlled by medication should not begin Pegasys monotherapy or Pegasys/ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Pegasys or Pegasys/ribavirin therapy.

Cardiovascular system
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alfa interferon therapies, including Pegasys. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of Pegasys 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 (see section 4.2).

Liver function
In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. Increases in ALT levels above baseline have been observed in patients treated with Pegasys, including patients with a viral response. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued (see sections 4.2 and 4.8).

In chronic hepatitis B, unlike chronic hepatitis C, disease exacerbations during therapy are not uncommon and are characterised by transient and potentially significant increases in serum ALT. In clinical trials with Pegasys in HBV, marked transaminase flares have been accompanied by mild changes in other measures of hepatic function and without evidence of hepatic decompensation. In approximately half the cases of flares exceeding 10 times the upper limit of normal, Pegasys dosing was reduced or withheld until the transaminase elevations subsided, while in the rest therapy was continued unchanged. More frequent monitoring of hepatic function was recommended in all instances.

Hypersensitivity
Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alfa 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 alfa 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 re-assessed (see also *Endocrine system* in sections 4.4 and 4.8).

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 (see section 4.8).

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 alfa interferons including Pegasys. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

Ocular changes
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 Pegasys. 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. Adult and paediatric patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during Pegasys therapy. Pegasys treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Pulmonary changes
Pulmonary symptoms, including dyspnoea, pulmonary infiltrates, pneumonia, and pneumonitis have been reported during therapy with Pegasys. In case of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.

Skin disorder
Use of alfa interferons has been associated with exacerbation or provocation of psoriasis and sarcoidosis. Pegasys 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 Pegasys and ribavirin treatment have not been established in patients with liver and other transplantations. Liver and renal graft rejections have been reported with Pegasys, alone or in combination with ribavirin.

HIV-HCV coinfection
Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with Pegasys with or without ribavirin. In study NR15961, patients concurrently treated with stavudine and interferon therapy with or without ribavirin, the incidence of pancreatitis and/or lactic acidosis was 3% (12/398).

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

Co-infected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with ribavirin in combination with interferons, including Pegasys. Baseline variables in co-infected cirrhotic patients that may be associated with hepatic decompensation include: increased serum bilirubin, decreased haemoglobin, increased alkaline phosphatase or decreased platelet count, and treatment with didanosine (ddI).

The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

During treatment, co-infected patients should be closely monitored for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function; e.g., Child-Pugh score of 7 or greater). The Child-Pugh scoring may be affected by factors related to treatment (i.e. indirect hyperbilirubinemia, decreased albumin) and not necessarily

attributable to hepatic decompensation. Treatment with Pegasys should be discontinued immediately in patients with hepatic decompensation.

In patients co-infected with HIV-HCV, limited efficacy and safety data are available in patients with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Pegasys and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Pegasys 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.

Use of peginterferon as long term maintenance monotherapy (unapproved use)
In a randomised, controlled US study (HALT-C) of HCV non-responder patients with varied degrees of fibrosis where 3.5 years of treatment with 90 micrograms/week of Pegasys monotherapy was studied, no significant reductions were observed in the rate of fibrosis progression or related clinical events.

Excipient
Pegasys contains benzyl alcohol. Must not be given to premature babies or neonates. May cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Administration of Pegasys 180 micrograms once weekly for 4 weeks in healthy male subjects did not show any effect on mephenytoin, dapsone, debrisoquine and tolbutamide pharmacokinetics profiles, suggesting that Pegasys has no effect on *in vivo* metabolic activity of cytochrome P450 3A4, 2C9, 2C19 and 2D6 isozymes.

In the same study, a 25% increase in the AUC of theophylline (marker of cytochrome P450 1A2 activity) was observed, demonstrating that Pegasys is an inhibitor of cytochrome P450 1A2 activity. Serum concentrations of theophylline should be monitored and appropriate dose adjustments of theophylline made for patients taking theophylline and Pegasys concomitantly. The interaction between theophylline and Pegasys is likely to be maximal after more than 4 weeks of Pegasys therapy.

HCV monoinfected patients and HBV monoinfected patients

In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95 mg; range 30 mg to 150 mg), treatment with Pegasys 180 micrograms sc once weekly for 4 weeks was associated with mean methadone levels that were 10% to 15% higher than at baseline. The clinical significance of this finding is unknown; nonetheless, patients should be monitored for the signs and symptoms of methadone toxicity. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of peginterferon alfa-2a and ribavirin concomitantly with azathioprin should be avoided. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicinal products should be stopped (see section 4.4).

Results from pharmacokinetic substudies of pivotal phase III trials demonstrated no pharmacokinetic interaction of lamivudine on Pegasys in HBV patients or between Pegasys and ribavirin in HCV patients.

A clinical trial investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration for the treatment of HBV, indicates that the combination is associated with an increased risk for developing peripheral neuropathy. The mechanism behind these events is not known; thus, co-treatment with telbivudine and other interferons (pegylated or standard) may also entail an excess risk. Moreover, the benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established. Therefore, the combination of Pegasys with telbivudine is contraindicated (see section 4.3).

HIV-HCV co-infected patients
No apparent evidence of drug interaction was observed in 47 HIV-HCV co-infected patients who completed a 12 week pharmacokinetic substudy to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine and zidovudine or stavudine). However, due to high variability, the confidence intervals were quite wide. Plasma exposure of ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).

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 (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral therapy regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of peginterferon alfa-2a in pregnant women. Studies in animals with interferon alfa-2a have shown reproductive toxicity (see section 5.3) and the potential risk for humans is unknown. Pegasys is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

It is unknown whether peginterferon alfa-2a/metabolites are excreted in human milk. Because of the potential for adverse reactions in breastfed infants, breastfeeding should be discontinued prior to initiation of treatment.

Fertility

There are no data on the effects of peginterferon alfa-2a on fertility in women. A prolongation of the menstrual cycle has been seen with peginterferon alfa-2a in female monkeys (see section 5.3).

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 Pegasys in

combination with ribavirin. Female patients of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded. Please refer to the ribavirin SmPC.

4.7 Effects on ability to drive and use machines

Pegasys has 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.

4.8 Undesirable effects

Summary of the safety profile

Chronic hepatitis C

The frequency and severity of the most commonly reported adverse reactions with Pegasys are similar to those reported with interferon alfa-2a (see Table 9).The most frequently reported adverse reactions with Pegasys 180 micrograms were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy.

Chronic hepatitis B

In clinical trials of 48 weeks treatment and 24 weeks follow-up, the safety profile for Pegasys in chronic hepatitis B was similar to that seen in chronic hepatitis C. With the exception of pyrexia the frequency of the majority of the reported adverse reactions was notably less in CHB patients treated with Pegasys monotherapy compared with HCV patients treated with Pegasys monotherapy (see Table 9). Adverse events were experienced by 88% of Pegasys-treated patients as compared with 53% of patients in the lamivudine comparator group, while 6% of the Pegasys-treated and 4% of the lamivudine-treated patients experienced serious adverse events during the studies. Adverse events or laboratory abnormalities led to 5% of patients withdrawing from Pegasys treatment, while less than 1% of patients withdrew from lamivudine treatment for these reasons. The percentage of patients with cirrhosis who withdrew from treatment was similar to that of the overall population in each treatment group.

Chronic hepatitis C in prior non-responder patients

Overall, the safety profile for Pegasys in combination with ribavirin in prior non-responder patients was similar to that in naïve patients. In a clinical trial of non-responder patients to prior pegylated interferon alfa-2b/ribavirin, which exposed patients to either 48 or 72 weeks of treatment, the frequency of withdrawal for adverse events or laboratory abnormalities from Pegasys treatment and ribavirin treatment was 6% and 7%, respectively, in the 48 week arms and 12% and 13% ,respectively, in the 72 week arms. Similarly for patients with cirrhosis or transition to cirrhosis, the frequencies of withdrawal from Pegasys treatment and ribavirin treatment were higher in the 72-week treatment arms (13% and 15%) than in the 48-week arms (6% and 6%). Patients who withdrew from previous therapy with pegylated interferon alfa-2b/ribavirin because of haematological toxicity were excluded from enrolling in this trial.

In another clinical trial, non-responder patients with advanced fibrosis or cirrhosis (Ishak score of 3 to 6) and baseline platelet counts as low as 50,000/mm^3 were treated for 48 weeks. Haematologic laboratory abnormalities observed during the first 20 weeks of the trial included anaemia (26% of patients experienced a haemoglobin level of <10 g/dl), neutropenia (30% experienced an ANC <750/mm^3), and thrombocytopenia (13% experienced a platelet count <50,000/ mm^3) (see section 4.4).

Chronic hepatitis C and HIV co-infection

In HIV-HCV co-infected patients, the clinical adverse reaction profiles reported for Pegasys, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients For HIV-HCV patients receiving Pegasys and ribavirin combination therapy other undesirable effects have been reported in ≥ 1% to ≤ 2% of patients: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia. Pegasys treatment was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of Pegasys had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data are available in co-infected patients with CD4+ cell counts <200/µl.

Tabulated list of adverse reactions

Table 9 summarises the undesirable effects reported with Pegasys monotherapy in CHB or CHC patients and with Pegasys in combination with ribavirin in CHC patients. Undesirable effects reported in clinical studies are grouped according to frequency as follows: 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). For spontaneous reports of undesirable effects from post-marketing experience, the frequency is not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

Table 9: Undesirable effects reported with Pegasys monotherapy for HBV or HCV or in combination with ribavirin for HCV patients in clinical trials and post marketing

Body system	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Infections and infestations		Bronchitis, upper respiratory infection, oral candidiasis, herpes simplex, fungal, viral and bacterial infections	Pneumonia, skin infection	Endocarditis, otitis externa		Sepsis
Neoplasms benign and malignant			Hepatic neoplasm			
Blood and lymphatic system disorders		Thrombocytopenia, anaemia, lymphadenopathy		Pancytopenia	Aplastic anaemia	Pure red cell aplasia
Immune system disorders			Sarcoidosis, thyroiditis	Anaphylaxis, systemic lupus erythematosus rheumatoid arthritis	Idiopathic or thrombotic thrombocytopenic purpura	Liver and renal graft rejection, Vogt-Koyanagi-Harada disease
Endocrine disorders		Hypothyroidism, hyperthyroidism	Diabetes	Diabetic ketoacidosis		
Metabolism and nutrition disorders	Anorexia		Dehydration			

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Psychiatric disorders	Depression*, anxiety, insomnia*	Aggression, mood alteration, emotional disorders, nervousness, libido decreased	Suicidal ideation, hallucinations	Suicide, psychotic disorder		Mania, bipolar disorders, homicidal ideation
Nervous system disorders	Headache, dizziness*, concentration impaired	Syncope, migraine, memory impairment, weakness, hypoaesthesia, hyperaesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence	Peripheral neuropathy	Coma, convulsions, facial palsy		Cerebral ischaemia
Eye disorders		Vision blurred, eye pain, eye inflammation, xerophthalmia	Retinal haemorrhage	Optic neuropathy, papilloedema, retinal vascular disorder, retinopathy, corneal ulcer	Vision loss	Serous retinal detachment
Ear and labyrinth disorders		Vertigo, earache	Hearing loss			
Cardiac disorders		Tachycardia, oedema peripheral, palpitations		Myocardial infarction, congestive heart failure, cardiomyopathy, angina, arrhythmia, atrial fibrillation, pericarditis, supraventricular tachycardia		
Vascular disorders		Flushing	Hypertension	Cerebral haemorrhage, vasculitis		Peripheral ischaemia
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		Pulmonary arterial hypertension[§]

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Gastrointestinal disorders	Diarrhoea*, nausea*, abdominal pain*	Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, dry mouth	Gastrointestinal bleeding	Peptic ulcer, pancreatitis		Ischaemic colitis, tongue pigmentation
Hepato-biliary disorders			Hepatic dysfunction	Hepatic failure, cholangitis, fatty liver		
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, pruritis, dry skin	Psoriasis, urticaria, eczema, rash, sweating increased, skin disorder, photosensitivity reaction, night sweats			Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, erythema multiforme	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps		Myositis		Rhabdomyolysis
Renal and urinary disorders				Renal insufficiency		
Reproductive system and breast disorders		Impotence				
General disorders and administration site conditions	Pyrexia, rigors*, pain*, asthenia, fatigue, injection site reaction*, irritability*	Chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst				
Investigations		Weight decreased				
Injury, poisoning and procedural complications				Substance overdose		

*These adverse reactions were common (**≥1/100 to < 1/10)** in CHB patients treated with Pegasys monotherapy

§ Class label for interferon products, see below Pulmonary arterial hypertension.

Description of selected adverse reactions

Pulmonary arterial hypertension
Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

Laboratory values
Pegasys treatment was associated with abnormal laboratory values: ALT increase, bilirubin increase, electrolyte disturbance (hypokalaemia, hypocalcaemia, hypophosphataemia), hyperglycaemia, hypoglycaemia and elevated triglycerides (see section 4.4.). With both Pegasys monotherapy, and also the combined treatment with ribavirin, up to 2% of patients experienced increased ALT levels that led to dose modification or discontinuation of the treatment.

Treatment with Pegasys was associated with decreases 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 (see sections 4.2 and 4.4).

Moderate (ANC: 0.749 - 0.5 x 10^9/l) and severe (ANC: < 0.5 x 10^9/l) neutropenia was observed respectively in 24% (216/887) and 5% (41/887) of patients receiving Pegasys 180 micrograms and ribavirin 1000/1200 milligrams for 48 weeks.

Anti-interferon antibodies
1-5% of patients treated with Pegasys developed neutralising anti-interferon antibodies. As with other interferons, a higher incidence of neutralising antibodies was seen in chronic hepatitis B. However in neither disease was this correlated with lack of therapeutic response.

Thyroid function
Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see section 4.4). The frequencies observed (4.9%) in patients receiving Pegasys/ribavirin (NV15801) are similar to those observed with other interferons.

Laboratory values for HIV-HCV co-infected patients
Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment. Decrease in ANC levels below 500 cells/mm^3 was observed in 13% and 11% of patients receiving Pegasys monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm^3 was observed in 10% and 8% of patients receiving Pegasys monotherapy and combination therapy, respectively. Anaemia (haemoglobin < 10 g/dl) was reported in 7% and 14% of patients treated with Pegasys monotherapy or in combination therapy, respectively.

Paediatric population

Chronic hepatitis C

In a clinical trial with 114 paediatric patients (5 to 17 years of age) treated with Pegasys alone or in combination with ribavirin (see section 5.1), dose modifications were required in approximately one-third of patients, most commonly for neutropenia and anaemia. In general, the safety profile observed in paediatric patients was similar to that seen in adults. In the paediatric study, the most prevalent adverse reactions in patients treated with combination therapy for up to 48 weeks with Pegasys and ribavirin were influenza-like illness (91%), headache (64%), gastrointestinal disorder (56%), , and injection-site reaction (45%). A full listing of adverse reactions reported in this treatment group (n=55) is provided in Table 10. Seven patients receiving combination Pegasys and ribavirin treatment for 48 weeks discontinued therapy for safety reasons (depression, psychiatric evaluation abnormal, transient

blindness, retinal exudates, hyperglycaemia, type 1 diabetes mellitus, and anaemia). Most of the adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 2 patients in the Pegasys plus ribavirin combination therapy group (hyperglycaemia and cholecystectomy).

Table 10: Adverse reactions reported among paediatric patients infected with HCV and assigned to Pegasys plus ribavirin in study NV17424

Body system	Very common	Common
Infections and infestations		Infectious mononucleosis, pharyngitis streptococcal, influenza, gastroenteritis viral, candidiasis, gastroenteritis, tooth abscess, hordeolum, urinary tract infection, nasopharyngitis
Blood and lymphatic system disorders		Anaemia
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia, type 1 diabetes mellitus
Psychiatric disorders	Insomnia	Depression, anxiety, hallucination, abnormal behaviour, aggression, anger, attention deficit / hyperactivity disorder
Nervous system disorders	Headache	Dizziness, disturbance in attention, migraine
Eye disorders		Blindness transient, retinal exudates, visual impairment eye irritation, eye pain, eye pruritis
Ear and labyrinth disorders		Ear pain
Respiratory, thoracic and mediastinal disorders		Dyspnoea, epistaxis
Gastrointestinal disorders	Gastrointestinal disorder	Abdominal pain upper, stomatitis, nausea, aphthous stomatitis, oral disorder
Skin and subcutaneous tissue disorders	Rash, pruritus, alopecia	Swollen face, drug eruption,
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Back pain, pain in extremity
Renal and urinary disorders		Dysuria, incontinence, urinary tract disorder
Reproductive system and breast disorders		Vaginal discharge
General disorders and administration site conditions	Influenza-like illness, injection site reaction, irritability, fatigue	Pyrexia, vessel puncture site haematoma, pain
Investigations		Psychiatric evaluation abnormal
Surgical and medical procedures		Tooth extraction, cholecystectomy
Social circumstances		Educational problem

Growth inhibition was observed in paediatric patients (see section 4.4). Paediatric patients treated with Pegasys plus ribavirin combination therapy showed a delay in weight and height increases after 48 weeks of therapy compared with baseline. Patient ‘weight for age’ and ‘height for age’ percentiles of the normative population decreased during treatment. At the end of 2 years follow-up after treatment, most patients had returned to baseline normative growth curve percentiles for weight and height (mean weight percentile was 64% at baseline and 60% at 2 years post-treatment; mean height percentile was 54% at baseline and 56% at 2 years post-treatment). At the end of treatment, 43% of patients experienced a weight percentile decrease of 15 percentiles or more, and 25% (13 of 53) experienced a height percentile decrease of 15 percentiles or more on the normative growth curves. At 2 years post-treatment, 16% (6 of 38) of patients remained 15 percentiles or more below their baseline weight curve and 11% (4 of 38) remained 15 percentiles or more below their baseline height curve.

55% (21 of 38) of subjects who completed the original study enrolled in the long-term follow up extending up to 6 years post-treatment. The study demonstrated that the post-treatment recovery in growth at 2 years post-treatment was maintained to 6 years post-treatment. For a few subjects who were more than 15 percentiles below their baseline height curve at 2 years post-treatment, they either returned to baseline comparable height percentiles at 6 years post-treatment or a non-treatment related causative factor has been identified. The extent of available data is not sufficient to conclude that growth inhibition due to Pegasys exposure is always reversible.

Laboratory values
Decreases in haemoglobin, neutrophils and platelets may require dose reduction or permanent discontinuation from treatment (see Table 3 and Table 7). Most laboratory abnormalities noted during the clinical trial returned to baseline levels shortly after discontinuation of treatment.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

Overdoses involving between two injections on consecutive days (instead of weekly interval) up to daily injections for 1 week (i.e., 1260 micrograms/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 micrograms have been administered in renal cell carcinoma and chronic myelogenous leukaemia clinical trials, respectively. Dose limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia, consistent with interferon therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB11

Mechanism of action

The conjugation of PEG reagent (bis-monomethoxypolyethylene glycol) to interferon alfa-2a forms a pegylated interferon alfa-2a (Pegasys). Pegasys possesses the *in vitro* antiviral and antiproliferative activities that are characteristic of interferon alfa-2a.

Interferon alfa-2a is conjugated with bis-[monomethoxy polyethylene glycol] at a degree of substitution of one mole of polymer/mole of protein. The average molecular mass is approximately 60,000 of which the protein moiety constitutes approximately 20,000.

Pharmacodynamic effects

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received treatment with 180 micrograms Pegasys. The first phase of decline occurs 24 to 36 hours after the first dose of Pegasys and is followed by the second phase of decline which continues over the next 4 to 16 weeks in patients who achieve a sustained response. Ribavirin had no significant effect on the initial viral kinetics over the first 4 to 6 weeks in patients treated with the combination of ribavirin and pegylated interferon alfa-2a or interferon alfa.

Clinical efficacy and safety

Chronic hepatitis B

All clinical trials recruited patients with chronic hepatitis B who had active viral replication measured by HBV DNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. Study WV16240 recruited patients who were positive for HBeAg, while study WV16241 recruited patients who were negative for HBeAg and positive for anti-HBe. In both studies the treatment duration was 48 weeks, with 24 weeks of treatment-free follow-up. Both studies compared Pegasys plus placebo vs Pegasys plus lamivudine vs lamivudine alone. No HBV-HIV co-infected patients were included in these clinical trials.

Response rates at the end of follow-up for the two studies are presented in Table 11. In study WV16240, the primary efficacy endpoints were HBeAg seroconversion and HBV-DNA below 10^5 copies/ml. In study WV16241, the primary efficacy endpoints were ALT normalisation and HBV-DNA below 2×10^4 copies/ml. HBV-DNA was measured by the COBAS AMPLICOR™ HBV MONITOR Assay (limit of detection 200 copies/ml).

A total of 283/1351 (21%) of patients had advanced fibrosis or cirrhosis, 85/1351 (6%) had cirrhosis. There was no difference in response rate between these patients and those without advanced fibrosis or cirrhosis.

Table 11: Serological, virological and biochemical responses in chronic hepatitis B

	HBeAg positive Study WV16240			**HBeAg negative / anti-HBe positive Study WV16241**		
Response Parameter	**Pegasys** 180 mcg & **Placebo** (N=271)	**Pegasys** 180 mcg & **Lamivudine** 100 mg (N=271)	**Lamivudine** 100 mg (N=272)	**Pegasys** 180 mcg & **Placebo** (N=177)	**Pegasys** 180 mcg & **Lamivudine** 100 mg (N=179)	**Lamivudine** 100 mg (N=181)
HBeAg Sero-conversion	32% #	27%	19%	N/A	N/A	N/A
HBV DNA response *	32% #	34%	22%	43% #	44%	29%
ALT Normal-isation	41% #	39%	28%	59% #	60%	44%
HBsAg Sero-conversion	3% #	3%	0%	3%	2%	0%

* For HBeAg-positive patients: HBV DNA < 10^5 copies/ml
For HBeAg-negative/anti-HBe-positive patients: HBV DNA < 2×10^4 copies/ml

p-value (vs. lamivudine) $\leq$ 0.01 (stratified Cochran-Mantel-Haenszel test)

Histological response was similar across the three treatment groups in each study; however, patients showing a sustained response 24 weeks after the end of treatment were significantly more likely to also show histological improvement.

All patients who completed the phase III studies were eligible for entry into a long-term follow-up study (WV16866). Among patients from study WV16240, who received Pegasys monotherapy and entered the long-term follow-up study, the rate of sustained HBeAg seroconversion 12 months after the end of therapy was 48% (73/153). In patients receiving Pegasys monotherapy in study WV16241, the rate of HBV DNA response and ALT normalisation 12 months after end of treatment were 42% (41/97) and 59% (58/99), respectively.

Chronic hepatitis C

Predictability of response
Please refer to section 4.2, in Table 2.

Dose-response in monotherapy
In a direct comparison with 90 micrograms, the 180 micrograms-dose was associated with superior sustained virological response in patients with cirrhosis, but in a study in non-cirrhotic patients very similar results were obtained with doses of 135 micrograms and 180 micrograms.

Confirmatory clinical trials in adult treatment-naïve patients
All clinical trials recruited interferon-naïve patients with chronic hepatitis C confirmed by detectable levels of serum HCV RNA, elevated levels of ALT (with the exception of study NR16071) and a liver biopsy consistent with chronic hepatitis. Study NV15495 specifically recruited patients with a histological diagnosis of cirrhosis (about 80%) or transition to cirrhosis (about 20%). Only HIV-HCV co-infected patients were included in the study NR15961 (see Table 20). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl.
For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see Tables 12, 13, 14 and Table 20, respectively. Virological response was defined as undetectable HCV RNA as measured by the COBAS AMPLICOR™ HCV Test, version 2.0 (limit of detection 100 copies/ml equivalent to 50 International Units/ml) and sustained response as one negative sample approximately 6 months after end of therapy.

Table 12: Virological response in HCV patients

	Pegasys monotherapy				**Pegasys combination therapy**		
	non-cirrhotic and cirrhotic		**cirrhotic**		**non-cirrhotic and cirrhotic**		
	Study NV15496 + NV15497 + NV15801		**Study NV15495**		**Study NV15942**	**Study NV15801**	
	Pegasys 180 mcg (N=701) 48 weeks	**Interferon alfa-2a** 6 MIU/3 MIU & 3 MIU (N=478) 48 weeks	**Pegasys** 180 mcg (N=87) 48 weeks	**Interferon alfa-2a** 3 MIU (N=88) 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg (N=436) 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg (N=453) 48 weeks	**Interferon alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg (N=444) 48 weeks
Response at End of Treatment	55 - 69%	22 - 28%	44%	14%	68%	69%	52%
Overall Sustained Response	28 - 39%	11 - 19%	30%*	8%*	63%	54%**	45%**

* 95% CI for difference: 11% to 33% p-value (stratified Cochran-Mantel-Haenszel test) = 0.001
** 95% CI for difference: 3% to 16% p-value (stratified Cochran-Mantel-Haenszel test) = 0.003

The virological responses of HCV monoinfected patients treated with Pegasys and ribavirin combination therapy in relation to genotype and pre-treatment viral load and in relation to genotype, pre-treatment viral load and rapid virological response at week 4 are summarised in Table 13 and Table 14, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype, baseline viral load and virological response at week 4 (see Tables 1, 13 and 14).

The difference between treatment regimens was in general not influenced by presence/absence of cirrhosis; therefore treatment recommendations for genotype 1, 2 or 3 are independent of this baseline characteristic.

Table 13: Sustained virological response based on genotype and pre-treatment viral load after Pegasys combination therapy with ribavirin in HCV patients

	Study NV15942				Study NV15801	
	Pegasys 180 mcg & **Ribavirin** 800 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Interferon alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg 48 weeks
Genotype 1	29% (29/101)	42% (49/118)* 52% (37/71)	41% (102/250)*	52% (142/271)* 65% (55/85)	45% (134/298) 53% (61/115)	36% (103/285) 44% (41/94)
Low viral load	41% (21/51)	26% (12/47)	55% (33/60)	47% (87/186)	40% (73/182)	33% (62/189)
High viral load	16% (8/50)		36% (69/190)			
Genotype 2/3	84% (81/96)	81% (117/144)	79% (78/99)	80% (123/153)	71% (100/140)	61% (88/145)
Low viral load	85% (29/34)	83% (39/47)	88% (29/33)	77% (37/48)	76% (28/37)	65% (34/52)
High viral load	84% (52/62)	80% (78/97)	74% (49/66)	82% (86/105)	70% (72/103)	58% (54/93)
Genotype 4	(0/5)	(8/12)	(5/8)	(9/11)	(10/13)	(5/11)

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
*Pegasys 180 mcg & ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg & ribavirin 800 mg, 48 w:
Odds Ratio (95% CI) = 1.52 (1.07 to 2.17), P-value (stratified Cochran-Mantel-Haenszel test) = 0.020
*Pegasys 180 mcg & ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg & ribavirin 1000/1200 mg, 24 w:
Odds Ratio (95% CI) = 2.12 (1.30 to 3.46), P-value (stratified Cochran-Mantel-Haenszel test) = 0.002.

The possibility to consider shortening treatment duration to 24 weeks in genotype 1 and 4 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response at week 4 in studies NV15942 and ML17131 (see Table 14).

Table 14: Sustained virological response based on rapid viral response at week 4 for genotype 1 and 4 after Pegasys combination therapy with ribavirin in HCV patients

	Study NV15942		Study ML17131
	Pegasys 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks
Genotype 1 RVR	90% (28/31)	92% (47/51)	77% (59/77)
Low viral load	93% (25/27)	96% (26/27)	80% (52/65)
High viral load	75% (3/4)	88% (21/24)	58% (7/12)
Genotype 1 non RVR	24% (21/87)	43% (95/220)	- -
Low viral load	27% (12/44)	50% (31/62)	-
High viral load	21% (9/43)	41% (64/158)	
Genotype 4 RVR	(5/6)	(5/5)	92% (22/24)
Genotype 4 non RVR	(3/6)	(4/6)	-

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24

Although limited, data indicated that shortening treatment to 24 weeks might be associated with a higher risk of relapse (see Table 15).

Table 15: Relapse of virological response at the end of treatment for rapid virological response population

	Study NV15942		Study NV15801
	Pegasys 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks
Genotype 1 RVR	6.7% (2/30)	4.3% (2/47)	0% (0/24)
Low viral load	3.8% (1/26)	0% (0/25)	0% (0/17)
High viral load	25% (1/4)	9.1% (2/22)	0% (0/7)
Genotype 4 RVR	(0/5)	(0/5)	0% (0/4)

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on a sustained virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 16).

In study NV17317 in patients infected with viral genotype 2 or 3, all patients received Pegasys 180 mcg sc qw and a ribavirin dose of 800 mg and were randomised to treatment for either 16 or 24 weeks. Overall treatment for 16 weeks resulted in lower sustained viral response (65%) than treatment for 24 weeks (76%) ($p < 0.0001$).

The sustained viral response achieved with 16 weeks of treatment and with 24 weeks of treatment was also examined in a retrospective subgroup analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline (see Table 16).

Table 16: Sustained virological response overall and based on rapid viral response by week 4 for genotype 2 or 3 after Pegasys combination therapy with ribavirin in HCV patients

Study NV17317				
	Pegasys 180 mcg & **Ribavirin** 800 mg 16 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	Treatment difference [95%CI]	p value
Genotype 2 or 3	65% (443/679)	76% (478/630)	-10.6% [-15.5% ; -0.06%]	P<0.0001
Genotype 2 or 3 RVR	82% (378/461)	90% (370/410)	-8.2% [-12.8% ; -3.7%]	P=0.0006
Low viral load	89% (147/166)	94% (141/150)	-5.4% [-12% ; 0.9%]	P=0.11
High viral load	78% (231/295)	88% (229/260)	-9.7% [-15.9% ;-3.6%]	P=0.002

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4

It is presently not clear whether a higher dose of ribavirin (e.g.1000/1200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The data indicated that shortening treatment to 16 weeks is associated with a higher risk of relapse (see Table 17).

Table 17: Relapse of virological response after the end of treatment in genotype 2 or 3 patients with a rapid viral response

Study NV17317				
	Pegasys 180 mcg & **Ribavirin** 800 mg 16 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	Treatment difference [95%CI]	p value
Genotype 2 or 3 RVR	15% (67/439)	6% (23/386)	9.3% [5.2% ; 13.6%]	P<0.0001
Low viral load	6% (10/155)	1% (2/141)	5% [0.6% ; 10.3%]	P=0.04
High viral load	20% (57/284)	9% (21/245)	11.5% [5.6% ; 17.4%]	P=0.0002

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
RVR = rapid viral response (HCV RNA undetectable) at week 4

Superior efficacy of Pegasys compared to interferon alfa-2a was demonstrated also in terms of histological response, including patients with cirrhosis and/or HIV-HCV co-infection.

Adult chronic hepatitis C prior treatment non-responder patients
In study MV17150, patients who were non-responders to previous therapy with pegylated interferon alfa-2b plus ribavirin were randomised to four different treatments:

- Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 60 weeks
- Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 36 weeks
- Pegasys 180 mcg/week for 72 weeks
- Pegasys 180 mcg/week for 48 weeks

All patients received ribavirin (1000 or 1200 mg/day) in combination with Pegasys. All treatment arms had 24 week treatment-free follow-up.

Multiple regression and pooled group analyses evaluating the influence of treatment duration and use of induction dosing clearly identified treatment duration for 72 weeks as the primary driver for achieving a sustained virological response. Differences in sustained virological response (SVR) based on treatment duration, demographics and best responses to previous treatment are displayed in Table 18.

Table 18: Week 12 virological response (VR) and sustained virological response (SVR) in patients with virological response at week 12 after treatment with Pegasys and ribavirin combination therapy in nonresponders to peginterferon alfa-2b plus ribavirin

Study MV17150			
	Pegasys 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 72 or 48 Weeks (N = 942) **Pts with VR at Wk 12** [a] **(N = 876)**	**Pegasys** 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 72 Weeks (N = 473) **SVR in Pts with VR at Wk 12** [b] **(N = 100)**	**Pegasys** 360/180 or 180 mcg & **Ribavirin** 1000/1200 mg 48 Weeks (N = 469) **SVR in Pts with VR at Wk 12** [b] **(N = 57)**
Overall	18% (157/876)	57% (57/100)	35% (20/57)
Low viral load	35% (56/159)	63% (22/35)	38% (8/21)
High viral load	14% (97/686)	54% (34/63)	32% (11/34)
Genotype 1/4	17% (140/846)	55% (52/94)	35% (16/46)
Low viral load	35% (54/154)	63% (22/35)	37% (7/19)
High viral load	13% (84/663)	52% (30/58)	35% (9/26)
Genotype 2/3	58% (15/26)	(4/5)	(3/10)
Low viral load	(2/5)	—	(1/2)
High viral load	(11/19)	(3/4)	(1/7)
Cirrhosis Status			
Cirrhosis	8% (19/239)	(6/13)	(3/6)
Noncirrhosis	22% (137/633)	59% (51/87)	34% (17/50)
Best Response during Previous Treatment			
$\geq 2\log_{10}$ decline in HCV RNA	28% (34/121)	68% (15/22)	(6/12)
$<2\log_{10}$ decline in HCV RNA	12% (39/323)	64% (16/25)	(5/14)
Missing best previous response	19% (84/432)	49% (26/53)	29% (9/31)

High viral load = > 800,000 IU/ml, low viral load = ≤ 800,000 IU/ml.

[a] Patients who achieved viral suppression (undetectable HCV RNA, < 50 IU/ml) at week 12 were considered to have a virological response at week 12. Patients missing HCV RNA results at week 12 have been excluded from the analysis.

[b] Patients who achieved viral suppression at week 12 but were missing HCV RNA results at the end of follow-up were considered to be non-responders.

In the HALT-C study, patients with chronic hepatitis C and advanced fibrosis or cirrhosis who were non-responders to previous treatment with interferon alfa or pegylated interferon alfa monotherapy or in combination therapy with ribavirin were treated with Pegasys 180 mcg/week and ribavirin 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on Pegasys plus ribavirin combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. The probability for sustained virological response varied depending upon the previous treatment regimen; see Table 19.

Table 19: Sustained virological response in HALT-C by previous treatment regimen in non-responder population

Previous Treatment	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks
Interferon	27% (70/255)
Pegylated interferon	34% (13/38)
Interferon plus ribavirin	13% (90/692)
Pegylated interferon plus ribavirin	11% (7/61)

HIV-HCV co-infected patients
The virological responses of patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and pre-treatment viral load for HIV-HCV co-infected patients are summarised below in Table 20.

Table 20: Sustained virological response based on genotype and pre-treatment viral load after Pegasys combination therapy with ribavirin in HIV-HCV co-infected patients

Study NR15961			
	Interferon alfa-2a 3 MIU & **Ribavirin 800 mg** 48 weeks	**Pegasys** 180 mcg & **Placebo** 48 weeks	**Pegasys** 180 mcg & **Ribavirin 800 mg** 48 weeks
All patients	12% (33/285)*	20% (58/286)*	40% (116/289)*
Genotype 1 Low viral load High viral load	7% (12/171) 19% (8/42) 3% (4/129)	14% (24/175) 38% (17/45) 5% (7/130)	29% (51/176) 61% (28/46) 18% (23/130)
Genotype 2-3 Low viral load High viral load	20% (18/89) 27% (8/30) 17% (10/59)	36% (32/90) 38% (9/24) 35% (23/66)	62% (59/95) 61% (17/28) 63% (42/67)

Low viral load = ≤ 800,000 IU/ml; High viral load = > 800,000 IU/ml
* Pegasys 180 mcg & ribavirin 800 mg vs. Interferon alfa-2a 3 MIU & ribavirin 800 mg:
Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001
* Pegasys 180 mcg & ribavirin 800 mg vs. Pegasys 180 mcg:
Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001
* Interferon alfa-2a 3 MIU & ribavirin 800 mg vs. Pegasys 180 mcg:
Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared treatment using Pegasys 180 mcg/week and either ribavirin 800 mg or 1000 mg (<75 kg)/1200 mg (≥75 kg) daily for 48 weeks. The study was not powered for efficacy considerations. The safety profiles in both ribavirin groups were consistent with the known safety profile of Pegasys plus ribavirin combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose ribavirin arm.

HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomised to receive Pegasys 180 micrograms/week and ribavirin 800 milligrams/day for either 24 or 48 weeks followed by a 24 week treatment free follow-up period or no treatment for 72 weeks. The SVRs reported in the treatment arms of this study were similar to the corresponding treatment arms from study NV15942.

Paediatric population
In the investigator sponsored CHIPS study (Chronic Hepatitis C International Paediatric Study), 65 children and adolescents (6-18 years) with chronic HCV infection were treated with Pegasys 100 mcg/m^2 sc once weekly and ribavirin 15 mg/kg/day for 24 weeks (genotypes 2 and 3) or 48 weeks (all other genotypes). Preliminary and limited safety data demonstrated no obvious departure from the known safety profile of the combination in adults with chronic HCV infection, but, importantly, the potential impact on growth has not been reported. Efficacy results were similar to those reported in adults.

In the NV17424 (PEDS-C) study, previously untreated paediatric patients 5 to 17 years of age (55% <12 years old) with compensated chronic hepatitis C and detectable HCV RNA were treated with Pegasys 180 mcg x BSA/1.73 m^2 once weekly for 48 weeks with or without ribavirin 15 mg/kg/day. All patients were followed for 24 weeks post-treatment. A total of 55 patients received initial combination treatment of Pegasys plus ribavirin, of whom 51% were female, 82% were Caucasian, and 82% were infected with HCV genotype 1. The study efficacy results for these patients are summarised in Table 21.

Table 21: Sustained virological response in the NV17424 study

	Pegasys 180 mcg x BSA/1.73 m² + Ribavirin 15 mg/kg (N=55)*
All HCV genotypes**	29 (53%)
HCV genotype 1	21/45 (47%)
HCV genotype 2 and 3	8/10 (80%)

*Results indicate undetectable HCV-RNA defined as HCV RNA less than 50 IU/ml at 24 weeks post-treatment using the AMPLICOR HCV test v2.
**Scheduled treatment duration was 48 weeks regardless of the genotype

5.2 Pharmacokinetic properties

Absorption
Following a single subcutaneous injection of Pegasys 180 micrograms in healthy subjects, serum concentrations of peginterferon alfa-2a are measurable within 3 to 6 hours. Within 24 hours, about 80% of the peak serum concentration is reached. The absorption of Pegasys is sustained with peak serum concentrations reached 72 to 96 hours after dosing. The absolute bioavailability of Pegasys is 84% and is similar to that seen with interferon alfa-2a.

Distribution
Peginterferon alfa-2a is found predominantly in the bloodstream and extracellular fluid as seen by the volume of distribution at steady-state (V_d) of 6 to 14 litres in humans after intravenous administration. From mass balance, tissue distribution and whole body autoradioluminography studies performed in rats, peginterferon alfa-2a is distributed to the liver, kidney and bone marrow in addition to being highly concentrated in the blood.

Biotransformation
The metabolism of Pegasys is not fully characterised; however studies in rats indicate that the kidney is a major organ for excretion of radiolabelled material.

Elimination
In humans, the systemic clearance of peginterferon alfa-2a is about 100-fold lower than that of the native interferon alfa-2a. After intravenous administration, the terminal half-life of peginterferon alfa-2a in healthy subjects is approximately 60 to 80 hours compared to values of 3-4 hours for standard interferon. The terminal half-life after subcutaneous administration in patients is longer with a mean value of 160 hours (84 to 353 hours). The terminal half-life may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

Linearity/non-linearity
Dose-proportional increases in exposure of Pegasys are seen in healthy subjects and in patients with chronic hepatitis B or C after once-weekly dosing.

In chronic hepatitis B or C patients, peginterferon alfa-2a serum concentrations accumulate 2 to 3 fold after 6 to 8 weeks of once weekly dosing compared to single dose values. There is no further accumulation after 8 weeks of once weekly dosing. The peak to trough ratio after 48 weeks of treatment is about 1.5 to 2. Peginterferon alfa-2a serum concentrations are sustained throughout one full week (168 hours).

Patients with renal impairment
A clinical trial evaluated 50 CHC patients with either moderate (creatinine clearance 30 to 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment, or with end stage renal disease (ESRD) requiring chronic hemodialysis (HD). Patients with moderate renal impairment receiving

Pegasys 180 mcg once weekly exhibited similar peginterferon alfa-2a plasma exposures compared to patients with normal renal function. Patients with severe renal impairment receiving Pegasys 180 mcg once weekly showed a 60% higher peginterferon alfa-2a exposure than patients with normal renal function, therefore a reduced dose of Pegasys 135 mcg once weekly is recommended in patients with severe renal impairment. In 13 patients with ESRD requiring chronic HD, administration of Pegasys 135 mcg once weekly resulted in 34% lower peginterferon alfa-2a exposure than in patients with normal renal function. However, several independent studies have demonstrated the 135mcg dose to be safe, efficacious and well tolerated, in patients with ESRD. (see section 4.2).

Gender
The pharmacokinetics of Pegasys after single subcutaneous injections was comparable between male and female healthy subjects.

Paediatric population
In a population pharmacokinetic study (NR16141), 14 children 2 to 8 years of age with CHC received Pegasys monotherapy at a dose of: 180 mcg x BSA of the child/1.73 m^2. The PK model developed from this study shows a linear influence of BSA on the apparent clearance of the drug over the age range studied. Thus, the lower the BSA of the child, the lower the clearance of the drug and the higher the resultant exposure. The mean exposure (AUC) during the dosing interval is predicted to be 25% to 70% higher than that observed in adults receiving 180 mcg fixed dosing.

Elderly
In subjects older than 62 years, the absorption of Pegasys after a single subcutaneous injection of 180 micrograms was delayed but still sustained compared to young healthy subjects (t_{max} of 115 hours vs. 82 hours, older than 62 years vs. younger, respectively). The AUC was slightly increased (1663 vs. 1295 ng·h/ml) but peak concentrations (9.1 vs. 10.3 ng/ml) were similar in subjects older than 62 years. Based on drug exposure, pharmacodynamic response and tolerability, a lower dose of Pegasys is not needed in the geriatric patient (see section 4.2).

Hepatic impairment
The pharmacokinetics of Pegasys were similar between healthy subjects and patients with hepatitis B or C. Comparable exposure and pharmacokinetic profiles were seen in cirrhotic (Child-Pugh Grade A) and non-cirrhotic patients.

Site of administration
Subcutaneous administration of Pegasys should be limited to the abdomen and thigh, as the extent of absorption based on AUC was about 20% to 30% higher upon injection in the abdomen and thigh. Exposure to Pegasys was decreased in studies following administration of Pegasys in the arm compared to administration in the abdomen and thigh.

5.3 Preclinical safety data

The non-clinical toxicity studies conducted with Pegasys were limited due to species specificity of interferons. Acute and chronic toxicity studies have been carried out in cynomolgus monkeys, and the findings observed in peginterferon dosed animals were similar in nature to those produced by interferon alfa-2a.

Reproductive toxicity studies have not been performed with Pegasys. As with other alfa interferons, prolongation of the menstrual cycle was observed following administration of peginterferon alfa-2a to female monkeys. Treatment with interferon alfa-2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys. Although no teratogenic effects were seen in the offspring delivered at term, adverse effects in humans cannot be excluded.

Pegasys plus ribavirin
When used in combination with ribavirin, Pegasys did not cause any effects in monkeys not previously seen with either active substance alone. The major treatment-related change was reversible mild to

moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Polysorbate 80
Benzyl alcohol
Sodium acetate
Acetic acid
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-8°C). Do not freeze.
Keep the pre-filled pen 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 (siliconised Type I glass) with a fixed needle (stainless steel), plunger stopper (butyl rubber laminated with fluororesin) and a needle shield (polyisoprene) in a pre-filled pen.
Available in packs containing 1, 4 or 12 pre-filled pens. Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution for injection is for single use only. It should be inspected visually for particulate matter and discoloration before administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Comprehensive instructions for the preparation and administration of Pegasys in pre-filled pen are given in the package leaflet.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

Pegasys 135 micrograms solution for injection in pre-filled pen
EU/1/02/221/011
EU/1/02/221/012
EU/1/02/221/013

Pegasys 180 micrograms solution for injection in pre-filled pen
EU/1/02/221/014
EU/1/02/221/015
EU/1/02/221/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2002
Date of latest renewal: 20 June 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Roche Diagnostics GmbH
Nonnenwald 2
D-82377 Penzberg
Germany

Name and address of the manufacturer(s) responsible for batch release

Roche Pharma AG
Emil-Barell-Str. 1
D-79639 Grenzach- Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)
The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 1 x 135 µg VIAL

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 1 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 vial
135 micrograms/1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 4 x 135 µg VIALS

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 1 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, (see leaflet for further information) sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
4 vials
135 micrograms/1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

135 μg VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pegasys 135 mcg injection
Peginterferon alfa-2a
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

135 mcg/1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 1 x 180 µg VIAL

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 1 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 vial
180 micrograms/1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 4 x 180 μg VIALS

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 1 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
4 vials
180 micrograms/1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

180 µg VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pegasys 180 mcg injection
Peginterferon alfa-2a
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

180 mcg/1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 1 x 90 µg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 90 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 90 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe + 1 injection needle
90 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/017

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 90 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

90 µg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pegasys 90 mcg injection
Peginterferon alfa-2a
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mcg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 1 x 135 μg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled syringe + 1 injection needle
135 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 4 x 135 μg PRE-FILLED SYRINGES

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for futher information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
4 pre-filled syringes + 4 injection needles
135 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 6 x 135 μg PRE-FILLED SYRINGES (WITHOUT BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for futher information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
6 pre-filled syringes + 6 injection needles
135 micrograms/0.5 ml
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/009

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 12 x 135 µg PRE-FILLED SYRINGES (WITH BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 12 (2 packs of 6) pre-filled syringes + 12 injection needles
135 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/009

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

135 μg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pegasys 135 mcg injection
Peginterferon alfa-2a
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

135 mcg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 1 x 180 µg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled syringe + 1 injection needle
180 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 4 x 180 µg PRE-FILLED SYRINGES

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
4 pre-filled syringes + 4 injection needles
180 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/008

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 6 x 180 μg PRE-FILLED SYRINGES (WITHOUT BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
6 pre-filled syringes + 6 injection needles
180 micrograms/0.5 ml
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/010

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 12 x 180 µg PRE-FILLED SYRINGES (WITH BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 12 (2 packs of 6) pre-filled syringes + 12 injection needles
180 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled syringe in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/010

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

180 μg PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pegasys 180 mcg injection
Peginterferon alfa-2a
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

180 mcg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 1 x 135 μg PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled pen
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled pen
135 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/011

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 4 x 135 μg PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled pen
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
4 pre-filled pens
135 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/012

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 12 x 135 μg PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled pen
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 0.5 ml solution contains 135 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
12 pre-filled pens
135 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/013

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 135 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

135 μg PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pegasys 135 mcg injection
Peginterferon alfa-2a
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

135 mcg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 1 x 180 μg PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection in pre-filled pen
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled pen
180 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/014

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 4 x 180 µg PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection in pre-filled pen
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
4 pre-filled pens
180 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/015

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 12 x 180 μg PRE-FILLED PENS

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection in pre-filled pen
Peginterferon alfa-2a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 0.5 ml solution contains 180 micrograms peginterferon alfa-2a.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol (see leaflet for further information), sodium acetate, acetic acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
12 pre-filled pens
180 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/016

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pegasys 180 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

180 μg PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pegasys 180 mcg injection
Peginterferon alfa-2a
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

180 mcg/0.5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Pegasys 135 micrograms solution for injection
Pegasys 180 micrograms solution for injection
Peginterferon alfa-2a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pegasys is and what it is used for

Pegasys contains the active substance peginterferon alfa-2a, which is a long-acting interferon. Interferon is a protein that modifies the response of the body's immune system to help fight infections and severe diseases. Pegasys is used to treat chronic hepatitis B or chronic hepatitis C in adults. It is also used to treat chronic hepatits C in children and adolescents aged 5 years and older, who have not been treated before. Both chronic hepatitis B and C are viral infections of the liver.

Chronic Hepatitis B: Pegasys is usually used alone.
Chronic Hepatitis C: Pegasys is used in combination with other medicines, for the treatment of chronic hepatitis C (CHC).

Refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

2. What you need to know before you use Pegasys

Do not use Pegasys
- if you are allergic to peginterferon alfa-2a, to any interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have ever had a heart attack or have been hospitalised for serious chest pains in the last six months.
- if you have, so called autoimmune hepatitis.
- if you have advanced liver disease and your liver does not work properly (e.g. your skin has become yellow).
- if the patient is a child less than 3 years old.
- if the patient is a child who has ever had serious psychiatric conditions such as severe depression or thoughts of committing suicide.
- if you are infected with both the hepatitis C virus and the human immunodeficiency virus, and your liver does not work properly (e.g. your skin has become yellow).
- if you are being treated with telbivudine, a medicine for hepatitis B infection (see “Other medicines and Pegasys”).

Warnings and precautions
Talk to your doctor, or pharmacist or nurse before using Pegasys
- if you have had a severe nervous or mental disorder.
- if you have ever had depression or symptoms associated with depression (e.g. feelings of sadness, dejection, etc.).
- if you are an adult who has or had a history of substance abuse (e.g. alcohol or drugs)
- if you have psoriasis, it may get worse during treatment with Pegasys.
- if you have a problem with your liver other than hepatitis B or C.
- if you have diabetes or high blood pressure, your doctor may ask you to have an eye examination.
- if you have been told you have VKH syndrome.
- if you have thyroid disease that is not well controlled with medicines.
- if you have ever had anaemia.
- if you have had an organ transplant (liver or kidney) or have one planned in the near future.
- if you are coinfected with HIV and treated with anti HIV medicinal products.
- if you have been withdrawn from previous therapy for Hepatitis C because of anaemia or low blood count.

Once you have started Pegasys treatment, talk to your doctor, nurse or pharmacist:
- if you develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) (see section 4).
- if you notice a change in your vision.
- if you develop symptoms associated with a cold or other respiratory infection (such as cough, fever or any difficulty in breathing).
- if you think you are getting an infection (such as pneumonia) as when receiving Pegasys you may temporarily have a greater risk of getting an infection.
- if you develop any signs of bleeding or unusual bruising, check with your doctor immediately.
- if you develop signs of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while on this medication, seek medical help immediately.
- if you develop symptoms of Vogt-Koyanagi-Harada syndrome; combination of complaints of neck stiffness, headache, loss of colour in skin or hair, eye disorders (such as blurred vision), and/or hearing abnormality (such as ringing in the ears).

During treatment your doctor will take blood samples regularly to check for changes in your white blood cells (cells that fight infection), red blood cells (cells that carry oxygen), platelets (blood clotting cells), liver function, glucose (blood sugar levels) or changes in other laboratory values.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Pegasys and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Pegasys with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Children and adolescents
Do not give this medicine to children below the age of 5 years. It has not been studied in combination with ribavirin in these children. Pegasys must not be given to children below the age of 3 years because it contains benzyl alcohol and may cause toxic reactions and allergic reactions in these children.
- **If your child has or has ever had a psychiatric disorder, talk to your doctor, who will monitor your child for signs or symptoms of depression (see section 4).**
- **When receiving Pegasys, your child may have slower growth and development (see section 4).**

Other medicines and Pegasys
Do not use Pegasys if you are taking telbivudine (see “Do not use Pegasys”) because the combination of these medicines increases the risk of developing peripheral neuropathy (numbness, tingling, and/or

burning sensations in the arms and/or legs). Therefore, the combination of Pegasys with telbivudine is contraindicated. Tell your doctor or pharmacist if you are being treated with telbivudine.
Tell your doctor if you are taking medicines for asthma, because the dose for your asthma medicine may need to be changed.

Patients who also have HIV infection: Tell your doctor if you are taking anti-HIV therapy. Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Pegasys + ribavirin may increase your risk of lactic acidosis or liver failure. Your doctor will monitor you for signs and symptoms of these conditions. Patients receiving zidovudine in combination with ribavirin and alfa interferons are at increased risk of developing anaemia. Patients receiving azathioprin in combination with ribavirin and peginterferon are at increased risk of developing severe blood disorders. Please be sure to read the ribavirin package leaflet also.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
When Pegasys is used in combination with ribavirin, both male and female patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur, as ribavirin can be very damaging to an unborn baby:
- if you are a **woman** of childbearing potential who is taking Pegasys in combination with ribavirin, you must have a negative pregnancy test before treatment, each month during therapy and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking the treatment and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking Pegasys in combination with ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now, but is of childbearing potential, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your partner must use an effective contraceptive during the time you are taking the treatment and for 7 months after stopping treatment. This can be discussed with your doctor.

Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Pegasys. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

Driving and using machines
Do not drive or use machines if you feel drowsy, tired, or confused while taking Pegasys.

Pegasys contains benzyl alcohol
Must not be given to premature babies, neonates or children up to 3 years old. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.

3. How to use Pegasys

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Pegasys dosing
Your doctor has determined the exact dose of Pegasys, and will tell you how often to use it. If necessary, the dose may be changed during treatment. Do not exceed the recommended dose.

Pegasys is used alone only if you cannot take ribavirin for any reason.

Pegasys given alone or in combination with ribavirin is usually given at a dose of 180 micrograms once a week.
The duration of combination treatment varies from 4 to 18 months depending on the type of virus you are infected with, on treatment response and whether you have been treated before. Please check with your doctor and follow the recommended duration of treatment.
Pegasys injection is normally taken at bedtime.

Use in children (5 years and older) and adolescents
Your doctor has determined the exact dose of Pegasys for your child and will tell you how often to use it. The usual dose of Pegasys, given in combination with ribavirin, is based on your child's height and weight. If necessary, the dose may be changed during treatment. It is recommended that Pegasys pre-filled syringes be used for children and adolescents, as they allow for dose adjustments. Do not exceed the recommended dose.

The duration of combination treatment in children varies from 6 to 12 months depending on the type of virus your child is infected with and their response to therapy. Please check with your doctor and follow the recommended duration of treatment. Pegasys injection is normally taken at bedtime.

Pegasys is intended for subcutaneous use (under the skin). This means that Pegasys is injected with a short needle into the fatty tissue under the skin in the abdomen or thigh. If you are injecting this medicine yourself, you will be instructed how to give the injection. Detailed instructions are provided at the end of this leaflet (see "How to inject Pegasys").

Use Pegasys exactly as described by your doctor, for as long as prescribed by your doctor.
If you have the impression that the effect of Pegasys is too strong or too weak, talk to your doctor or pharmacist.

Combination therapy with ribavirin in chronic hepatitis C
In the case of combination therapy with Pegasys and ribavirin, please follow the dosing regimen recommended by your doctor.

Combination therapy with other medicines in chronic hepatitis C
In the case of combination therapy with Pegasys, please follow the dosing regimen recommended by your doctor and refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

If you use more Pegasys than you should
Contact your doctor or pharmacist as soon as possible.

If you forget to take Pegasys
If you realise you missed your injection 1 or 2 days after it was scheduled, you should inject your recommended dose as soon as possible. Take your next injection on the regularly scheduled day.
If you realise you missed your injection 3 to 5 days after it was scheduled, you should take your injection at the recommended dose as soon as possible. Take your next doses at 5 day intervals until you return to your regularly scheduled day of the week.

> As an example: Your regular weekly Pegasys injection is on Monday. You remember on Friday that you forgot to take your injection on Monday (4 days late). You should inject your regularly scheduled dose immediately on Friday and take your next injection on Wednesday (5 days after your Friday dose). Your next injection will be on the Monday, 5 days later after the Wednesday injection. You are now back on your regularly scheduled day and should continue your injections every Monday.

If you realise you missed your injection 6 days after it was scheduled, you should wait and take your dose on the next day, your regularly scheduled day.
Contact your doctor or pharmacist if you need any help determining how to manage a missed dose of Pegasys.

Do not take a double dose to make up for a forgotten dose.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some people get depressed when taking Pegasys alone or in combination treatment with ribavirin, and in some cases people have had suicidal thoughts or aggressive behaviour (sometimes directed against others such as thoughts about threatening the life of the others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Growth and development (children and adolescents):
With up to one year of treatment with Pegasys in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. While most children returned to their projected height within two years after completing treatment, and the majority of the remaining children within six years after completing treatment, it remains possible that Pegasys may affect the final adult height.

Tell your doctor immediately if you notice any of the following side effects: severe chest pain; persistent cough; irregular heartbeat; trouble breathing; confusion; depression; severe stomach pain; blood in stool (or black, tarry stools); severe nosebleed; fever or chills; problems with your eyesight. These side effects can be serious and you may need urgent medical attention.

Very common side effects with the combination of Pegasys and ribavirin (may effect more than 1 in 10 people) are:

Metabolic disorders: Loss of appetite
Psychiatric and nervous system disorders: Feeling depressed (feeling low, feeling bad about yourself or feeling hopeless), anxiety, inability to sleep, headache, difficulty concentrating and dizziness
Breathing disorders: Cough, shortness of breath
Digestive system disorders: Diarrhoea, nausea, abdominal pain
Skin disorders: Loss of hair, and skin reactions (including itching, dermatitis and dry skin)
Muscle and bone disorders: Pain in joints and muscles
General disorders: Fever, weakness, tiredness, shaking, chills, pain, injection site irritation and irritability (getting easily upset)

Common side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 10 people) are:

Infections: Fungal, viral and bacterial infections. Upper respiratory infection, bronchitis, fungal infection of the mouth and herpes (a common recurring viral infection affecting the lips, mouth)
Blood disorders: Low platelet count (affecting the clotting ability), anaemia (low red cell count) and enlarged lymph glands
Hormone system disorders: Overactive and underactive thyroid gland
Psychiatric and nervous system disorders: Mood /emotion changes, aggression, nervousness, decreased sexual desire, poor memory, fainting, decreased muscle strength, migraine, numbness, tingling, burning sensation, tremor, changes in the sense of taste, nightmares, sleepiness
Eye disorders: Blurry vision, eye pain, eye inflammation and dry eyes
Ear disorders: ear pain
Heart and blood vessel disorders: Rapid heart rate, pulsation of the heart beats, swelling in the extremities, flushing

Breathing disorders: Shortness of breath with activity, nose bleeds, nose and throat inflammation, infections of the nose and sinuses (air-filled spaces found in the bones of the head and face), runny nose, sore throat
Digestive system disorders: Vomiting, indigestion, difficulty swallowing, mouth ulceration, bleeding gums, inflammation of tongue and mouth, flatulence (excess amount of air or gases), dry mouth and loss of weight
Skin disorders: Rash, increased sweating, psoriasis, hives, eczema, sensitivity to sunlight, night sweats
Muscle and bone disorders: Back pain, joint inflammation, muscle weakness, bone pain, neck pain, muscle pain, muscle cramps
Reproductive system disorders: Impotence (inability to maintain an erection)
General disorders: Chest pain, flu-like illness, malaise (not feeling well), lethargy, hot flushes, thirst

Uncommon side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 100 people) are:

Infections: Lung infection, skin infections
Neoplasms benign and malignant disorders: Liver tumour
Immune system disorders: Sarcoidosis (areas of inflamed tissue occurring throughout the body), inflammation of the thyroid
Hormone system disorders: Diabetes (high blood sugar)
Metabolic disorders: Dehydration
Psychiatric and nervous system disorders: Thoughts of suicide, hallucinations (severe problems with personality and deterioration in normal social functioning),peripheral neuropathy (disorder of the nerves affecting the extremities)
Eye disorders: Bleeding in the retina (back of the eye)
Ear disorders: Hearing loss
Heart and blood vessel disorders: High blood pressure
Breathing disorders: Wheezing
Digestive system disorders: Gastrointestinal bleeding
Liver disorders: Poor functioning of the liver

Rare side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 1000 people) are:

Infections: Infection of the heart, infection of the external ear
Blood disorders: Severe reduction in red blood cells, white blood cells and platelets
Immune system disorders: Severe allergic reaction, systemic lupus erythematosus (an illness where the body attacks its own cells), rheumatoid arthritis (an autoimmune disease)
Hormone system disorders: Diabetic ketoacidosis, a complication of uncontrolled diabetes
Psychiatric and nervous system disorders: Suicide, psychotic disorders (severe problems with personality and deterioration in normal social functioning), coma (a deep prolonged unconsciousness), seizures, facial palsy (weakness of the facial muscle)
Eye disorders: Inflammation and swelling of the optic nerve, inflammation of the retina, ulceration of the cornea
Heart and blood vessel disorders: Heart attack, heart failure, heart pain, rapid heart rhythm, rhythm disorders or inflammation of the lining of the heart and cardiac muscle, bleeding in the brain and inflammation in the vessels
Breathing disorders: Interstitial pneumonia (inflammation of the lungs including fatal outcome), blood clots in the lung
Digestive system disorders: Stomach ulcer, inflammation of the pancreas
Liver disorders: Liver failure, bile duct inflammation, fatty liver
Muscle and bone disorders: Inflammation of the muscles
Kidney disorders: Kidney failure
Injury or poisoning: Substance overdose

Very rare side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 10,000 people) are:

Blood disorders: Aplastic anaemia (failure of the bone marrow to produce red blood cells, white blood cells and platelets)
Immune system disorders: Idiopathic (or thrombotic) thrombocytopenic purpura (increased bruising, bleeding, decreased platelets, anaemia and extreme weakness)
Eye disorders: Loss of vision
Skin disorders: Toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degrees of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), angioedema (swelling in the skin and mucosa)

Side effects with unknown frequency:

Blood disorders: Pure red cell aplasia (a severe form of anaemia where red blood cell production is decreased or stopped); it can result in symptoms such as feeling very tired with no energy
Immune system disorders: Vogt Koyanagi Harada disease – a rare disease characterised by loss of vision, hearing and skin pigmentation; liver and kidney transplant rejections
Psychiatric and nervous system disorders: Mania (episodes of exaggerated elevation of mood) and bipolar disorders (episodes of exaggerated elevation of mood alternating with sadness and hopelessness); thoughts about threatening the life of others, stroke
Eye disorders: Rare form of retinal detachment with fluid in the retina
Heart and blood vessel disorders: Peripheral ischaemia (insufficient blood supply to the extremities)
Digestive system disorders: Ischaemic colitis (insufficient blood supply to the bowels), changes in the colour of the tongue
Muscle and bone disorders: Serious muscle damage and pain
Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with Pegasys.

When Pegasys is used alone in hepatitis B or C patients, some of these effects are less likely to occur.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pegasys

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

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

Do not use this medicine if you notice the vial or packaging is damaged, if the solution is cloudy or if it has floating particles or if the medicine is any colour besides colourless to light yellow.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pegasys contains

- The active substance is peginterferon alfa-2a. Each vial of 1.0 ml solution contains 135 or 180 micrograms peginterferon alfa-2a.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections.

What Pegasys looks like and contents of the pack

Pegasys is presented as a solution for injection in a vial (1 ml). It is available in packs containing 1 or 4 single dose vials. Not all pack-sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

How to inject Pegasys

The following instructions explain how to use Pegasys single dose vials to inject yourself or your child. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you on how to give the injections.

Getting ready

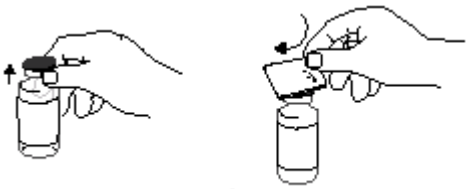
Wash your hand carefully before handling any of the items.

Collect the necessary items before beginning:
Included in the pack:
- a vial of Pegasys solution for injection

Not included in the pack:
- a 1 ml syringe
- a long needle to withdraw Pegasys from the vial
- a short needle for the subcutaneous injection
- a cleansing swab
- small bandage or sterile gauze
- an adhesive bandage
- a container for the waste material

Measuring the dose of Pegasys

- Remove the protective cap from the Pegasys vial (**1**).

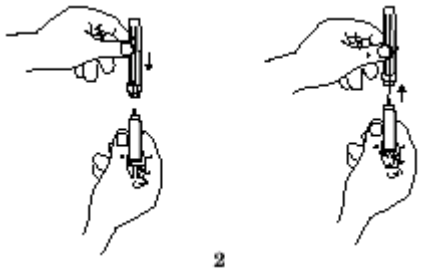


1

- Clean the rubber top of the vial with a cleansing swab.

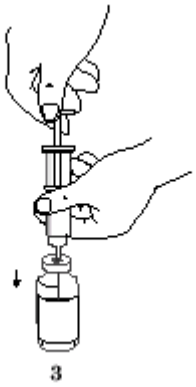
You can save the swab to clean the skin area where you will inject Pegasys.

- Remove the syringe from the wrapping. Do not touch the tip of the syringe.
- Take the long needle and place it firmly on to the tip of the syringe (**2**).



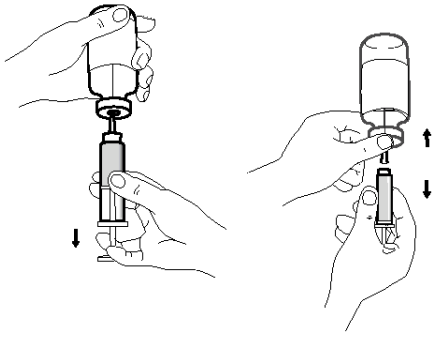
2

- Remove the needle guard without touching the needle and keep the syringe with the needle in your hand.
- Insert the needle through the rubber top of the Pegasys vial (**3**).



3

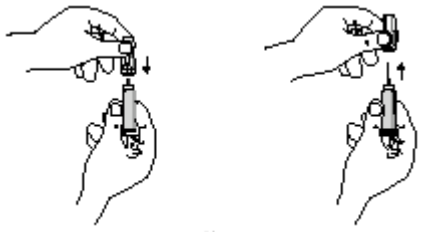
- Hold the vial and syringe in one hand and turn the vial and the syringe upside down (**4**).



4

With the syringe pointing up, make certain that the tip of the needle is in the Pegasys solution. Your other hand will be free to move the plunger of the syringe.

- Slowly pull back the plunger to withdraw a bit more than the dose prescribed by your doctor into the syringe.
- Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle while keeping the needle in the vial and without touching the tip of the syringe.
- Take the short needle and place it firmly on to the tip of the syringe (**5**).



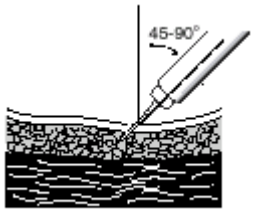
5

- Remove the needle guard from the syringe needle.
- Check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back. To remove air bubbles from the syringe, hold the syringe with the needle pointing up. Tap the syringe gently to bring the bubbles to the top. Push the plunger up slowly to the correct dose. Replace the needle guard and place the syringe in a horizontal position until ready for use.

- Allow the solution to reach room temperature before injection or warm the syringe between your palms.
- Visually inspect the solution prior to administration: do not use if it is discoloured or if particles are present. You are now ready to inject the dose.

Injecting the solution

- Select the injection site in the abdomen or thigh (except your navel or waistline). Change your injection site each time.
- Clean and disinfect the skin where the injection is to be made with a cleansing swab.
- Wait for the area to dry.
- Remove the needle guard.
- With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil.
- Insert the needle all the way into the pinched skin at an angle of 45° to 90° (**6**).



6

- Inject the solution by gently pushing the plunger all the way down.
- Pull the needle straight out of the skin.
- Press the injection site with a small bandage or sterile gauze if necessary for several seconds.

Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

Disposal of the injection materials

The syringe, needle and all injection materials are intended for single use and must be discarded after the injection. Dispose of the syringe and needle safely in a closed container. Ask your doctor, hospital or pharmacist for an appropriate container.

Package leaflet: Information for the user

Pegasys 90 micrograms solution for injection in pre-filled syringe
Pegasys 135 micrograms solution for injection in pre-filled syringe
Pegasys 180 micrograms solution for injection in pre-filled syringe
Peginterferon alfa-2a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pegasys is and what it is used for

Pegasys contains the active substance peginterferon alfa-2a, which is a long-acting interferon. Interferon is a protein that modifies the response of the body's immune system to help fight infections and severe diseases. Pegasys is used to treat chronic hepatitis B or chronic hepatitis C in adults. It is also used to treat chronic hepatits C in children and adolescents aged 5 years and older, who have not been treated before. Both chronic hepatitis B and C are viral infections of the liver.

Chronic Hepatitis B: Pegasys is usually used alone.
Chronic Hepatitis C: Pegasys is used in combination with other medicines, for the treatment of chronic hepatitis C (CHC).

Refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

2. What you need to know before you use Pegasys

Do not use Pegasys
- if you are allergic to peginterferon-alfa-2a, to any interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have ever had a heart attack or have been hospitalised for serious chest pains in the last six months.
- if you have, so called autoimmune hepatitis.
- if you have advanced liver disease and your liver does not work properly (e.g. your skin has become yellow).
- if the patient is a child less than 3 years old.
- if the patient is a child who has ever had serious psychiatric conditions such as severe depression or thoughts of committing suicide.
- if you are infected with both the hepatitis C virus and the human immunodeficiency virus, and your liver does not work properly (e.g. your skin has become yellow).
- if you are being treated with telbivudine, a medicine for hepatitis B infection (see “Other medicines and Pegasys”).

Warnings and precautions
Talk to your doctor , pharmacist or nurse before using Pegasys
- if you have had a severe nervous or mental disorder.
- if you have ever had depression or symptoms associated with depression (e.g. feelings of sadness, dejection, etc.).
- if you are an adult who has or had a history of substance abuse (e.g. alcohol or drugs)
- if you have psoriasis, it may get worse during treatment with Pegasys.
- if you have a problem with your liver other than hepatitis B or C.
- if you have diabetes or high blood pressure, your doctor may ask you to have an eye examination.
- if you have been told you have VKH syndrome.
- if you have thyroid disease that is not well controlled with medicines.
- if you have ever had anaemia.
- if you have had an organ transplant (liver or kidney) or have one planned in the near future.
- if you are coinfected with HIV and treated with anti HIV medicinal products.
- if you have been withdrawn from previous therapy for Hepatitis C because of anaemia or low blood count.

Once you have started Pegasys treatment, talk to your doctor, nurse or pharmacist:
- if you develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) (see section 4).
- if you notice a change in your vision.
- if you develop symptoms associated with a cold or other respiratory infection (such as cough, fever or any difficulty in breathing).
- if you think you are getting an infection (such as pneumonia) as when receiving Pegasys you may temporarily have a greater risk of getting an infection.
- if you develop any signs of bleeding or unusual bruising, check with your doctor immediately.
- if you develop signs of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while on this medication, seek medical help immediately.
- if you develop symptoms of Vogt-Koyanagi-Harada syndrome; combination of complaints of neck stiffness, headache, loss of colour in skin or hair, eye disorders (such as blurred vision), and/or hearing abnormality (such as ringing in the ears).

During treatment your doctor will take blood samples regularly to check for changes in your white blood cells (cells that fight infection), red blood cells (cells that carry oxygen), platelets (blood clotting cells), liver function, glucose (blood sugar levels) or changes in other laboratory values.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Pegasys and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Pegasys with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Children and adolescents
Do not give this medicine to children below the age of 5 years. It has not been studied in combination with ribavirin in these children. Pegasys must not be given to children below the age of 3 years because it contains benzyl alcohol and may cause toxic reactions and allergic reactions in these children.
- **If your child has or has ever had a psychiatric disorder, talk to your doctor, who will monitor your child for signs or symptoms of depression (see section 4).**
- **When receiving Pegasys, your child may have slower growth and development (see section 4).**

Other medicines and Pegasys
Do not use Pegasys if you are taking telbivudine (see “Do not use Pegasys”) because the combination of these medicines increases the risk of developing peripheral neuropathy (numbness, tingling, and/or

burning sensations in the arms and/or legs). Therefore, the combination of Pegasys with telbivudine is contraindicated. Tell your doctor or pharmacist if you are being treated with telbivudine.
Tell your doctor if you are taking medicines for asthma, because the dose for your asthma medicine may need to be changed.
Patients who also have HIV infection: Tell your doctor if you are taking anti-HIV therapy. Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Pegasys + ribavirin may increase your risk of lactic acidosis or liver failure. Your doctor will monitor you for signs and symptoms of these conditions. Patients receiving zidovudine in combination with ribavirin and alfa interferons are at increased risk of developing anaemia. Patients receiving azathioprin in combination with ribavirin and peginterferon are at increased risk of developing severe blood disorders. Please be sure to read the ribavirin package leaflet also.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
When Pegasys is used in combination with ribavirin, both male and female patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur, as ribavirin can be very damaging to an unborn baby:
- if you are a **woman** of childbearing potential who is taking Pegasys in combination with ribavirin, you must have a negative pregnancy test before treatment, each month during therapy and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking the treatment and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking Pegasys in combination with ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now, but is of childbearing potential, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your partner must use an effective contraceptive during the time you are taking the treatment and for 7 months after stopping treatment. This can be discussed with your doctor.

Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Pegasys. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

Driving and using machines
Do not drive or use machinery if you feel drowsy, tired, or confused while taking Pegasys.

Pegasys contains benzyl alcohol
Must not be given to premature babies, neonates or children up to 3 years old. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.

3. How to use Pegasys

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Pegasys dosing
Your doctor has determined the exact dose of Pegasys, and will tell you how often to use it. If necessary, the dose may be changed during treatment. Do not exceed the recommended dose.

Pegasys is used alone only if you cannot take ribavirin for any reason

Pegasys given alone or in combination with ribavirin is usually given at a dose of 180 micrograms once a week.
The duration of combination treatment varies from 4 to 18 months depending on the type of virus you are infected with, on treatment response and whether you have been treated before. Please check with your doctor and follow the recommended duration of treatment.
Pegasys injection is normally taken at bedtime.

Use in children (5 years and older) and adolescents
Your doctor has determined the exact dose of Pegasys for your child and will tell you how often to use it. The usual dose of Pegasys, given in combination with ribavirin, is based on your child's height and weight. If necessary, the dose may be changed during treatment. It is recommended that Pegasys pre-filled syringes be used for children and adolescents, as they allow for dose adjustments. Do not exceed the recommended dose.

The duration of combination treatment in children varies from 6 to 12 months depending on the type of virus your child is infected with and their response to therapy. Please check with your doctor and follow the recommended duration of treatment. Pegasys injection is normally taken at bedtime.

Pegasys is intended for subcutaneous use (under the skin). This means that Pegasys is injected with a short needle into the fatty tissue under the skin in the abdomen or thigh. If you are injecting this medicine yourself, you will be instructed how to give the injection. Detailed instructions are provided at the end of this leaflet (see "How to inject Pegasys").

Use Pegasys exactly as described by your doctor, for as long as prescribed by your doctor.
If you have the impression that the effect of Pegasys is too strong or too weak, talk to your doctor or pharmacist.

Combination therapy with ribavirin in chronic hepatitis C
In the case of combination therapy with Pegasys and ribavirin, please follow the dosing regimen recommended by your doctor.

Combination therapy with other medicines in chronic hepatitis C
In the case of combination therapy with Pegasys, please follow the dosing regimen recommended by your doctor and refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

If you use more Pegasys than you should
Contact your doctor or pharmacist as soon as possible.

If you forget to take Pegasys
If you realise you missed your injection 1 or 2 days after it was scheduled, you should inject your recommended dose as soon as possible. Take your next injection on the regularly scheduled day.
If you realise you missed your injection 3 to 5 days after it was scheduled, you should take your injection at the recommended dose as soon as possible. Take your next doses at 5 day intervals until you return to your regularly scheduled day of the week.

> As an example: Your regular weekly Pegasys injection is on Monday. You remember on Friday that you forgot to take your injection on Monday (4 days late). You should inject your regularly scheduled dose immediately on Friday and take your next injection on Wednesday (5 days after your Friday dose). Your next injection will be on the Monday, 5 days later after the Wednesday injection. You are now back on your regularly scheduled day and should continue your injections every Monday.

If you realise you missed your injection 6 days after it was scheduled, you should wait and take your dose on the next day, your regularly scheduled day.
Contact your doctor or pharmacist if you need any help determining how to manage a missed dose of Pegasys.

Do not take a double dose to make up for a forgotten dose.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some people get depressed when taking Pegasys alone or in combination treatment with ribavirin, and in some cases people have had suicidal thoughts or aggressive behaviour (sometimes directed against others such as thoughts about threatening the life of the others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Growth and development (children and adolescents):
With up to one year of treatment with Pegasys in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. While most children returned to their projected height within two years after completing treatment, and the majority of the remaining children within six years after completing treatment, it remains possible that Pegasys may affect the final adult height.

Tell your doctor immediately if you notice any of the following side effects: severe chest pain; persistent cough; irregular heartbeat; trouble breathing; confusion; depression; severe stomach pain; blood in stool (or black, tarry stools); severe nosebleed; fever or chills; problems with your eyesight. These side effects can be serious and you may need urgent medical attention.

Very common side effects with the combination of Pegasys and ribavirin (may affect more than 1 in 10 people) are:

Metabolic disorders: Loss of appetite
Psychiatric and nervous system disorders: Feeling depressed (feeling low, feeling bad about yourself or feeling hopeless), anxiety, inability to sleep, headache, difficulty concentrating and dizziness
Breathing disorders: Cough, shortness of breath
Digestive system disorders: Diarrhoea, nausea, abdominal pain
Skin disorders: Loss of hair, and skin reactions (including itching, dermatitis and dry skin)
Muscle and bone disorders: Pain in joints and muscles
General disorders: Fever, weakness, tiredness, shaking, chills, pain, injection site irritation and irritability (getting easily upset)

Common side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 10 people) are:

Infections: Fungal, viral and bacterial infections. Upper respiratory infection, bronchitis, fungal infection of the mouth and herpes (a common recurring viral infection affecting the lips, mouth)
Blood disorders: Low platelet count (affecting the clotting ability), anaemia (low red cell count) and enlarged lymph glands
Hormone system disorders: Overactive and underactive thyroid gland
Psychiatric and nervous system disorders: Mood /emotion changes, aggression, nervousness, decreased sexual desire, poor memory, fainting, decreased muscle strength, migraine, numbness, tingling, burning sensation, tremor, changes in the sense of taste, nightmares, sleepiness
Eye disorders: Blurry vision, eye pain, eye inflammation and dry eyes
Ear disorders: ear pain
Heart and blood vessel disorders: Rapid heart rate, pulsation of the heart beats, swelling in the extremities, flushing

Breathing disorders: Shortness of breath with activity, nose bleeds, nose and throat inflammation, infections of the nose and sinuses (air-filled spaces found in the bones of the head and face), runny nose, sore throat
Digestive system disorders: Vomiting, indigestion, difficulty swallowing, mouth ulceration, bleeding gums, inflammation of tongue and mouth, flatulence (excess amount of air or gases), dry mouth and loss of weight
Skin disorders: Rash, increased sweating, psoriasis, hives, eczema, sensitivity to sunlight, night sweats
Muscle and bone disorders: Back pain, joint inflammation, muscle weakness, bone pain, neck pain, muscle pain, muscle cramps
Reproductive system disorders: Impotence (inability to maintain an erection)
General disorders: Chest pain, flu-like illness, malaise (not feeling well), lethargy, hot flushes, thirst

Uncommon side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 100 people) are:

Infections: Lung infection, skin infections
Neoplasms benign and malignant disorders: Liver tumour
Immune system disorders: Sarcoidosis (areas of inflamed tissue occurring throughout the body), inflammation of the thyroid
Hormone system disorders: Diabetes (high blood sugar)
Metabolic disorders: Dehydration
Psychiatric and nervous system disorders: Thoughts of suicide, hallucinations (severe problems with personality and deterioration in normal social functioning), peripheral neuropathy (disorder of the nerves affecting the extremities)
Eye disorders: Bleeding in the retina (back of the eye)
Ear disorders: Hearing loss
Heart and blood vessel disorders: High blood pressure
Breathing disorders: Wheezing
Digestive system disorders: Gastrointestinal bleeding
Liver disorders: Poor functioning of the liver

Rare side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 1000 people) are:

Infections: Infection of the heart, infection of the external ear
Blood disorders: Severe reduction in red blood cells, white blood cells and platelets
Immune system disorders: Severe allergic reaction, systemic lupus erythematosus (an illness where the body attacks its own cells), rheumatoid arthritis (an autoimmune disease)
Hormone system disorders: Diabetic ketoacidosis, a complication of uncontrolled diabetes
Psychiatric and nervous system disorders: Suicide, psychotic disorders (severe problems with personality and deterioration in normal social functioning), coma (a deep prolonged unconsciousness), seizures, facial palsy (weakness of the facial muscle)
Eye disorders: Inflammation and swelling of the optic nerve, inflammation of the retina, ulceration of the cornea
Heart and blood vessel disorders: Heart attack, heart failure, heart pain, rapid heart rhythm, rhythm disorders or inflammation of the lining of the heart and cardiac muscle, bleeding in the brain and inflammation in the vessels
Breathing disorders: Interstitial pneumonia (inflammation of the lungs including fatal outcome), blood clots in the lung
Digestive system disorders: Stomach ulcer, inflammation of the pancreas
Liver disorders: Liver failure, bile duct inflammation, fatty liver
Muscle and bone disorders: Inflammation of the muscles
Kidney disorders: Kidney failure
Injury or poisoning: Substance overdose

Very rare side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 10,000 people) are:

Blood disorders: Aplastic anaemia (failure of the bone marrow to produce red blood cells, white blood cells and platelets)
Immune system disorders: Idiopathic (or thrombotic) thrombocytopenic purpura (increased bruising, bleeding, decreased platelets, anaemia and extreme weakness)
Eye disorders: Loss of vision
Skin disorders: Toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degrees of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), angioedema (swelling in the skin and mucosa)

Side effects with unknown frequency:

Blood disorders: Pure red cell aplasia (a severe form of anemia where red blood cell production is decreased or stopped); it can result in symptoms such as feeling very tired with no energy
Immune system disorders: Vogt Koyanagi Harada disease – a rare disease characterised by loss of vision, hearing and skin pigmentation; liver and kidney transplant rejections
Psychiatric and nervous system disorders: Mania (episodes of exaggerated elevation of mood) and bipolar disorders (episodes of exaggerated elevation of mood alternating with sadness and hopelessness); thoughts about threatening the life of others, stroke
Eye disorders: Rare form of retinal detachment with fluid in the retina
Heart and blood vessel disorders: Peripheral ischaemia (insufficient blood supply to the extremities)
Digestive system disorders: Ischaemic colitis (insufficient blood supply to the bowels), changes in the colour of the tongue
Muscle and bone disorders: Serious muscle damage and pain
Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with Pegasys.

When Pegasys is used alone in hepatitis B or C patients, some of these effects are less likely to occur

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pegasys

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

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

Do not use this medicine if you notice the syringe or needle packaging is damaged, if the solution is cloudy or if it has floating particles or if the medicine is any colour besides colourless to light yellow.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pegasys contains

- The active substance is peginterferon alfa-2a. Each pre-filled syringe of 0.5 ml solution contains 90, 135 or 180 micrograms peginterferon alfa-2a.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections.

What Pegasys looks like and contents of the pack

Pegasys is presented as a solution for injection in a pre-filled syringe (0.5 ml) with a separate injection needle.

Pegasys 90 micrograms solution for injection in pre-filled syringe
The syringe contains graduation marks corresponding to 90 micrograms (mcg), 65 mcg, 45 mcg, 30 mcg, 20 mcg and 10 mcg. It is available in packs containing 1 pre-filled syringe.

Pegasys 135 micrograms solution for injection in pre-filled syringe
The syringe contains graduation marks corresponding to 135 micrograms (mcg), 90 mcg and 45 mcg. It is available in packs containing containing 1, 4 or a multipack of 12 (2 packs of 6) pre-filled syringes. Not all pack-sizes may be marketed.

Pegasys 180 micrograms solution for injection in pre-filled syringe
The syringe contains graduation marks corresponding to 180 micrograms (mcg), 135 mcg and 90 mcg. It is available in packs containing containing 1, 4 or a multipack of 12 (2 packs of 6) pre-filled syringes. Not all pack-sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

How to inject Pegasys
The following instructions explain how to use Pegasys pre-filled syringes to inject yourself or your child. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you on how to give the injections.

Getting ready

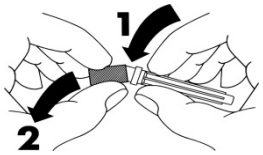
Wash your hands carefully before handling any of the items.

Collect the necessary items before beginning:
Included in the pack:
- a pre-filled syringe of Pegasys
- an injection needle

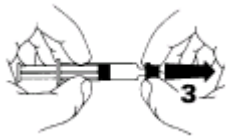
Not included in the pack:
- a cleansing swab
- small bandage or sterile gauze
- an adhesive bandage
- a container for the waste material

Preparing the syringe and needle for injection

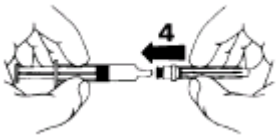
- Remove the protective cap that covers the back of the needle (**1**-**2**).



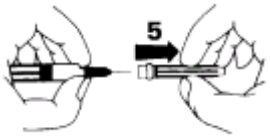
- Remove the rubber cap from the syringe (**3**). Do not touch the tip of the syringe.



- Place the needle firmly on the tip of the syringe (**4**).



- Remove the needle guard from the syringe needle (**5**).

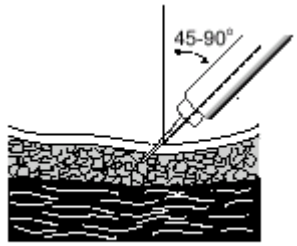


- To remove air bubbles from the syringe, hold the syringe with the needle pointing up. Tap the syringe gently to bring the bubbles to the top. Push the plunger up slowly to the correct dose. Replace the needle guard and place the syringe in a horizontal position until ready for use.
- Allow the solution to reach room temperature before injection or warm the syringe between your palms.
- Visually inspect the solution prior to administration: do not use if it is discoloured or if particles are present.

You are now ready to inject the dose.

Injecting the solution

- Select the injection site in the abdomen or thigh (except your navel or waistline). Change your injection site each time.
- Clean and disinfect the skin where the injection is to be made with a cleansing swab.
- Wait for the area to dry.
- Remove the needle guard.
- With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil.
- Insert the needle all the way into the pinched skin at an angle of 45° to 90° (**6**).



6

- Inject the solution by gently pushing the plunger all the way down.
- Pull the needle straight out of the skin.
- Press the injection site with a small bandage or sterile gauze if necessary for several seconds.

Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

Disposal of the injection materials

The syringe, needle and all injection materials are intended for single use and must be discarded after the injection. Dispose of the syringe and needle safely in a closed container. Ask your doctor, hospital or pharmacist for an appropriate container.

Package leaflet: Information for the user

Pegasys 135 micrograms solution for injection in pre-filled pen
Pegasys 180 micrograms solution for injection in pre-filled pen
Peginterferon alfa-2a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pegasys is and what it is used for

Pegasys contains the active substance peginterferon alfa-2a, which is a long-acting interferon. Interferon is a protein that modifies the response of the body's immune system to help fight infections and severe diseases. Pegasys is used to treat chronic hepatitis B or chronic hepatitis C in adults. It is also used to treat chronic hepatits C in children and adolescents aged 5 years and older, who have not been treated before. Both chronic hepatitis B and C are viral infections of the liver.

Chronic Hepatitis B: Pegasys is usually used alone.
Chronic Hepatitis C: Pegasys is used in combination with other medicines, for the treatment of chronic hepatitis C (CHC).

Refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

2. What you need to know before you use Pegasys

Do not use Pegasys
- if you are allergic to peginterferonalfa-2a, to any interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have ever had a heart attack or have been hospitalised for serious chest pains in the last six months.
- if you have, so called autoimmune hepatitis.
- if you have advanced liver disease and your liver does not work properly (e.g. your skin has become yellow).
- if the patient is a child less than 3 years old.
- if the patient is a child who has ever had serious psychiatric conditions such as severe depression or thoughts of committing suicide.
- if you are infected with both the hepatitis C virus and the human immunodeficiency virus, and your liver does not work properly (e.g. your skin has become yellow).
- if you are being treated with telbivudine, a medicine for hepatitis B infection (see “Other medicines and Pegasys”).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Pegasys
- if you have had a severe nervous or mental disorder.
- if you have ever had depression or symptoms associated with depression (e.g. feelings of sadness, dejection, etc.).
- if you are an adult who has or had a history of substance abuse (e.g. alcohol or drugs)
- if you have psoriasis, it may get worse during treatment with Pegasys.
- if you have a problem with your liver other than hepatitis B or C.
- if you have diabetes or high blood pressure, your doctor may ask you to have an eye examination.
- if you have been told you have VKH syndrome.
- if you have thyroid disease that is not well controlled with medicines.
- if you have ever had anaemia.
- if you have had an organ transplant (liver or kidney) or have one planned in the near future.
- if you are coinfected with HIV and treated with anti HIV medicinal products.
- if you have been withdrawn from previous therapy for Hepatitis C because of anaemia or low blood count.

Once you have started Pegasys treatment, talk to your doctor, nurse or pharmacist:
- if you develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc.) (see section 4).
- if you notice a change in your vision.
- if you develop symptoms associated with a cold or other respiratory infection (such as cough, fever or any difficulty in breathing).
- if you think you are getting an infection (such as pneumonia) as when receiving Pegasys you may temporarily have a greater risk of getting an infection.
- if you develop any signs of bleeding or unusual bruising, check with your doctor immediately.
- if you develop signs of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while on this medication, seek medical help immediately.
- if you develop symptoms of Vogt-Koyanagi-Harada syndrome; combination of complaints of neck stiffness, headache, loss of colour in skin or hair, eye disorders (such as blurred vision), and/or hearing abnormality (such as ringing in the ears).

During treatment your doctor will take blood samples regularly to check for changes in your white blood cells (cells that fight infection), red blood cells (cells that carry oxygen), platelets (blood clotting cells), liver function, glucose (blood sugar levels) or changes in other laboratory values.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving Pegasys and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of Pegasys with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Children and adolescents
Do not give this medicine to children below the age of 5 years. It has not been studied in combination with ribavirin in these children. Pegasys must not be given to children below the age of 3 years because it contains benzyl alcohol and may cause toxic reactions and allergic reactions in these children.
- **If your child has or has ever had a psychiatric disorder, talk to your doctor, who will monitor your child for signs or symptoms of depression (see section 4).**
- **When receiving Pegasys, your child may have slower growth and development (see section 4).**

Other medicines and Pegasys
Do not use Pegasys if you are taking telbivudine (see “Do not use Pegasys”) because the combination of these medicines increases the risk of developing peripheral neuropathy (numbness, tingling, and/or

burning sensations in the arms and/or legs). Therefore, the combination of Pegasys with telbivudine is contraindicated. Tell your doctor or pharmacist if you are being treated with telbivudine.
Tell your doctor if you are taking medicines for asthma, because the dose for your asthma medicine may need to be changed.
Patients who also have HIV infection: Tell your doctor if you are taking anti-HIV therapy. Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of Pegasys + ribavirin may increase your risk of lactic acidosis or liver failure. Your doctor will monitor you for signs and symptoms of these conditions. Patients receiving zidovudine in combination with ribavirin and alfa interferons are at increased risk of developing anaemia. Patients receiving azathioprin in combination with ribavirin and peginterferon are at increased risk of developing severe blood disorders. Please be sure to read the ribavirin package leaflet also.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
When Pegasys is used in combination with ribavirin, both male and female patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur, as ribavirin can be very damaging to an unborn baby:
- if you are a **woman** of childbearing potential who is taking Pegasys in combination with ribavirin, you must have a negative pregnancy test before treatment, each month during therapy and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking the treatment and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking Pegasys in combination with ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now, but is of childbearing potential, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your partner must use an effective contraceptive during the time you are taking the treatment and for 7 months after stopping treatment. This can be discussed with your doctor.

Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking Pegasys. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

Refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

Driving and using machines
Do not drive or use machinery if you feel drowsy, tired, or confused while taking Pegasys.

Pegasys contains benzyl alcohol
Must not be given to premature babies, neonates or children up to 3 years old. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.

3. How to use Pegasys

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Pegasys dosing
Your doctor has determined the exact dose of Pegasys, and will tell you how often to use it. If necessary, the dose may be changed during treatment. Do not exceed the recommended dose.

Pegasys is used alone only if you cannot take ribavirin for any reason

Pegasys given alone or in combination with ribavirin is usually given at a dose of 180 micrograms once a week.
The duration of combination treatment varies from 4 to 18 months depending on the type of virus you are infected with, on treatment response and whether you have been treated before. Please check with your doctor and follow the recommended duration of treatment.
Pegasys injection is normally taken at bedtime.

Use in children (5 years and older) and adolescents
Your doctor has determined the exact dose of Pegasys for your child and will tell you how often to use it. The usual dose of Pegasys, given in combination with ribavirin, is based on your child's height and weight. If necessary, the dose may be changed during treatment. It is recommended that Pegasys pre-filled syringes be used for children and adolescents, as they allow for dose adjustments. Pegasys pre-filled pens should not be used by children and adolescents who require doses less than 135 micrograms. Do not exceed the recommended dose.

The duration of combination treatment in children varies from 6 to 12 months depending on the type of virus your child is infected with and their response to therapy. Please check with your doctor and follow the recommended duration of treatment. Pegasys injection is normally taken at bedtime.

Pegasys is intended for subcutaneous use (under the skin). This means that Pegasys is injected with a short needle into the fatty tissue under the skin in the abdomen or thigh. If you are injecting this medicine yourself, you will be instructed how to give the injection. Detailed instructions are provided at the end of this leaflet (see "How to inject Pegasys").

Use Pegasys exactly as described by your doctor, for as long as prescribed by your doctor.
If you have the impression that the effect of Pegasys is too strong or too weak, talk to your doctor or pharmacist.

Combination therapy with ribavirin in chronic hepatitis C
In the case of combination therapy with Pegasys and ribavirin, please follow the dosing regimen recommended by your doctor.

Combination therapy with other medicines in chronic hepatitis C
In the case of combination therapy with Pegasys, please follow the dosing regimen recommended by your doctor and refer also to the package leaflets of any other medicines that are used in combination with Pegasys.

If you use more Pegasys than you should
Contact your doctor or pharmacist as soon as possible.

If you forget to take Pegasys
If you realise you missed your injection 1 or 2 days after it was scheduled, you should inject your recommended dose as soon as possible. Take your next injection on the regularly scheduled day.
If you realise you missed your injection 3 to 5 days after it was scheduled, you should take your injection at the recommended dose as soon as possible. Take your next doses at 5 day intervals until you return to your regularly scheduled day of the week.

> As an example: Your regular weekly Pegasys injection is on Monday. You remember on Friday that you forgot to take your injection on Monday (4 days late). You should inject your regularly scheduled dose immediately on Friday and take your next injection on Wednesday (5 days after your Friday dose). Your next injection will be on the Monday, 5 days later after the Wednesday injection. You are now back on your regularly scheduled day and should continue your injections every Monday.

If you realise you missed your injection 6 days after it was scheduled, you should wait and take your dose on the next day, your regularly scheduled day.
Contact your doctor or pharmacist if you need any help determining how to manage a missed dose of Pegasys.

Do not take a double dose to make up for a forgotten dose.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some people get depressed when taking Pegasys alone or in combination treatment with ribavirin, and in some cases people have had suicidal thoughts or aggressive behaviour (sometimes directed against others such as thoughts about threatening the life of the others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Growth and development (children and adolescents):
With up to one year of treatment with Pegasys in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. While most children returned to their projected height within two years after completing treatment, and the majority of the remaining children within six years after completing treatment, it remains possible that Pegasys may affect the final adult height.

Tell your doctor immediately if you notice any of the following side effects: severe chest pain; persistent cough; irregular heartbeat; trouble breathing; confusion; depression; severe stomach pain; blood in stool (or black, tarry stools); severe nosebleed; fever or chills; problems with your eyesight. These side effects can be serious and you may need urgent medical attention.

Very common side effects with the combination of Pegasys and ribavirin (may affect more than 1 in 10 people) are:

Metabolic disorders: Loss of appetite
Psychiatric and nervous system disorders: Feeling depressed (feeling low, feeling bad about yourself or feeling hopeless), anxiety, inability to sleep, headache, difficulty concentrating and dizziness
Breathing disorders: Cough, shortness of breath
Digestive system disorders: Diarrhoea, nausea, abdominal pain
Skin disorders: Loss of hair, and skin reactions (including itching, dermatitis and dry skin)
Muscle and bone disorders: Pain in joints and muscles
General disorders: Fever, weakness, tiredness, shaking, chills, pain, injection site irritation and irritability (getting easily upset)

Common side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 10 people) are:

Infections: Fungal, viral and bacterial infections. Upper respiratory infection, bronchitis, fungal infection of the mouth and herpes (a common recurring viral infection affecting the lips, mouth)
Blood disorders: Low platelet count (affecting the clotting ability), anaemia (low red cell count) and enlarged lymph glands
Hormone system disorders: Overactive and underactive thyroid gland
Psychiatric and nervous system disorders: Mood /emotion changes, aggression, nervousness, decreased sexual desire, poor memory, fainting, decreased muscle strength, migraine, numbness, tingling, burning sensation, tremor, changes in the sense of taste, nightmares, sleepiness
Eye disorders: Blurry vision, eye pain, eye inflammation and dry eyes
Ear disorders: ear pain
Heart and blood vessel disorders: Rapid heart rate, pulsation of the heart beats, swelling in the extremities, flushing

Breathing disorders: Shortness of breath with activity, nose bleeds, nose and throat inflammation, infections of the nose and sinuses (air-filled spaces found in the bones of the head and face), runny nose, sore throat
Digestive system disorders: Vomiting, indigestion, difficulty swallowing, mouth ulceration, bleeding gums, inflammation of tongue and mouth, flatulence (excess amount of air or gases), dry mouth and loss of weight
Skin disorders: Rash, increased sweating, psoriasis, hives, eczema, sensitivity to sunlight, night sweats
Muscle and bone disorders: Back pain, joint inflammation, muscle weakness, bone pain, neck pain, muscle pain, muscle cramps
Reproductive system disorders: Impotence (inability to maintain an erection)
General disorders: Chest pain, flu-like illness, malaise (not feeling well), lethargy, hot flushes, thirst

Uncommon side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 100 people) are:

Infections: Lung infection, skin infections
Neoplasms benign and malignant disorders: Liver tumour
Immune system disorders: Sarcoidosis (areas of inflamed tissue occurring throughout the body), inflammation of the thyroid
Hormone system disorders: Diabetes (high blood sugar)
Metabolic disorders: Dehydration
Psychiatric and nervous system disorders: Thoughts of suicide, hallucinations (severe problems with personality and deterioration in normal social functioning), peripheral neuropathy (disorder of the nerves affecting the extremities)
Eye disorders: Bleeding in the retina (back of the eye)
Ear disorders: Hearing loss
Heart and blood vessel disorders: High blood pressure
Breathing disorders: Wheezing
Digestive system disorders: Gastrointestinal bleeding
Liver disorders: Poor functioning of the liver

Rare side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 1000 people) are:

Infections: Infection of the heart, infection of the external ear
Blood disorders: Severe reduction in red blood cells, white blood cells and platelets
Immune system disorders: Severe allergic reaction, systemic lupus erythematosus (an illness where the body attacks its own cells), rheumatoid arthritis (an autoimmune disease)
Hormone system disorders: Diabetic ketoacidosis, a complication of uncontrolled diabetes
Psychiatric and nervous system disorders: Suicide, psychotic disorders (severe problems with personality and deterioration in normal social functioning), coma (a deep prolonged unconsciousness), seizures, facial palsy (weakness of the facial muscle)
Eye disorders: Inflammation and swelling of the optic nerve, inflammation of the retina, ulceration of the cornea
Heart and blood vessel disorders: Heart attack, heart failure, heart pain, rapid heart rhythm, rhythm disorders or inflammation of the lining of the heart and cardiac muscle, bleeding in the brain and inflammation in the vessels
Breathing disorders: Interstitial pneumonia (inflammation of the lungs including fatal outcome), blood clots in the lung
Digestive system disorders: Stomach ulcer, inflammation of the pancreas
Liver disorders: Liver failure, bile duct inflammation, fatty liver
Muscle and bone disorders: Inflammation of the muscles
Kidney disorders: Kidney failure
Injury or poisoning: Substance overdose

Very rare side effects with the combination of Pegasys and ribavirin (may affect up to 1 in 10,000 people) are:

Blood disorders: Aplastic anaemia (failure of the bone marrow to produce red blood cells, white blood cells and platelets)
Immune system disorders: Idiopathic (or thrombotic) thrombocytopenic purpura (increased bruising, bleeding, decreased platelets, anaemia and extreme weakness)
Eye disorders: Loss of vision
Skin disorders: Toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degrees of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), angioedema (swelling in the skin and mucosa)

Side effects with unknown frequency:

Blood disorders: Pure red cell aplasia (a severe form of anemia where red blood cell production is decreased or stopped); it can result in symptoms such as feeling very tired with no energy
Immune system disorders: Vogt Koyanagi Harada disease – a rare disease characterised by loss of vision, hearing and skin pigmentation; liver and kidney transplant rejections
Psychiatric and nervous system disorders: Mania (episodes of exaggerated elevation of mood) and bipolar disorders (episodes of exaggerated elevation of mood alternating with sadness and hopelessness); thoughts about threatening the life of others, stroke
Eye disorders: Rare form of retinal detachment with fluid in the retina
Heart and blood vessel disorders: Peripheral ischaemia (insufficient blood supply to the extremities)
Digestive system disorders: Ischaemic colitis (insufficient blood supply to the bowels), changes in the colour of the tongue
Muscle and bone disorders: Serious muscle damage and pain
Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with Pegasys.

When Pegasys is used alone in hepatitis B or C patients, some of these effects are less likely to occur.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pegasys

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

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

Do not use this medicine if you notice the pre-filled pen or packaging is damaged, if the solution is cloudy or if it has floating particles or if the medicine is any colour besides colourless to light yellow.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pegasys contains

- The active substance is peginterferon alfa-2a. Each pre-filled pen of 0.5 ml solution contains 135or 180 micrograms peginterferon alfa-2a.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections.

What Pegasys looks like and contents of the pack

Pegasys is presented as a solution for injection in a pre-filled pen (0.5 ml). It is available in packs containing 1, 4 or 12 pre-filled pens. Not all pack-sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

How to inject Pegasys

It is important to read, understand and follow these instructions so that you or your caregiver use the pre-filled pen correctly. These instructions do not replace training from your healthcare provider. Ask your healthcare provider any questions you may have. Do not attempt to administer an injection until you are sure that you understand how to use the pre-filled pen.

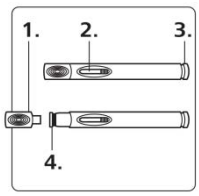
The Pegasys pre-filled pen is intended to be used in a home-setting by patients who have been properly instructed. The device is for single use only and is then to be discarded.

Do not:

- attempt to open or dismantle the pre-filled pen.
- expose to excessive forces or shock.
- use through clothing covering the skin.
- use if pre-filled pen appears to be damaged.
- use if medicine is cloudy, hazy, discoloured or has particles in it.
- shake
- remove the cap until you are ready to inject.
- try to re-use the pre-filled pen.
- manipulate the needle-shield before, during or after use, as this is a safety device.

Pre-filled pen components

1. Cap
2. Viewing window
3. Activation button
4. Needle-shield (only visible once cap is removed in Step 5)



What you will need:

Pegasys pre-filled pen
Alcohol pad
A puncture-proof container with lid for safe disposal of used pens

List of subsections on how to proceed:

1) Visually check the pre-filled pen
2) Allow the pre-filled pen to adjust to room temperature
3) Clean your hands
4) Choose and prepare an injection site
5) Remove cap
6) Place pre-filled pen on injection site
7) Give injection
8) Dispose of pre-filled pen

1) Visually check the pre-filled pen

Take the pre-filled pen out of the refrigerator. Do not shake.
Visually examine the pre-filled pen, as well as the medicine through the viewing window.

Dispose of the pre-filled pen and use another if:

- the medicine is cloudy
- the medicine contains particles
- the medicine is any colour besides colourless to light yellow
- any part of the pre-filled pen appears to be damaged
- the expiration date has passed. You will find the expiration date on the box as well as on the label of the pre-filled pen itself.

Keep the protective cap on the pre-filled pen until Step 5.

2) Allow the pre-filled pen to adjust to room temperature

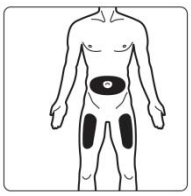
Allow the refrigerated pre-filled pen to adjust to room temperature for about 20 minutes. Do not warm up pre-filled pen in any other way.

3) Clean your hands

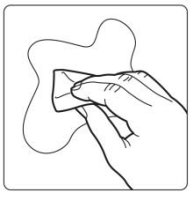
Wash your hands well using soap and water.

4) Choose and prepare an injection site

Choose a place on your stomach or thigh (see the picture). Avoid your navel and areas that could be irritated by a belt or waistband. You should use a different place each time you give yourself an injection.



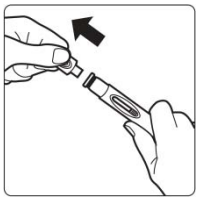
Clean the area using the alcohol pad and put the pad aside to wipe the site again after injection, if necessary. Let the skin dry for 10 seconds. Be sure not to touch the cleaned area prior to injection.



5) Remove cap

Hold the pre-filled pen firmly with one hand and pull off the protective cap with the other hand. You may see a small drop(s) or loss of some liquid coming out of the pen. This is normal.

NOTE: The cap contains a loose-fitting metal tube. Once the cap is removed, the pre-filled pen should be used immediately. If it is not used within 5 minutes, the pre-filled pen should be disposed and a new pre-filled pen should be used. Never re-attach protective cap after removal.



6) Place the pre-filled pen on the injection site

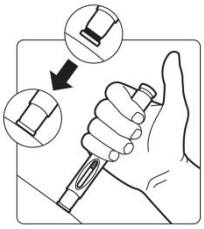
Hold the pre-filled pen comfortably in your hand. Pinch and hold a fold of skin at the injection site with your free hand, such that the needle-shield can rest on the skin-fold firmly and safely.

Place pre-filled pen straight up on the skin fold at a right angle (90°) on the injection site.

NOTE: Do not yet attempt to press the activation button.

Press the pre-filled pen firmly against the skin until the needle-shield is completely pushed into the pen.

→ *The pre-filled pen is now unlocked and ready for injection.*



7) Give injection

While holding pre-filled pen firmly in place, press the activation button with your thumb and **immediately release the button.**

→ *A "click" sound will indicate the start of the injection.*

→ *The red indicator will move down in the viewing window as the injection is ongoing.*

Keep the pre-filled pen pressed on the skin for **10 seconds** for injection to complete.

→ *You might hear a second "click" as the activation button pops back up.*

→ *The viewing window will now be completely red.*

Make sure you have taken your thumb off the activation button. Lift the pre-filled pen straight up (90° angle).

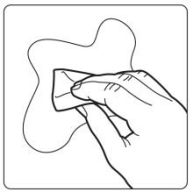
→ *The needle-shield will automatically move out and lock to prevent needle injuries.*

CAUTION:
If the viewing window is not completely filled by the red indicator,

- the needle-shield may not have locked.
    - Do not touch the tip of the pre-filled pen, since needlestick injuries may occur.

- you may not have received an entire dose.
    - Do not try to use the pre-filled pen again
    - Do not repeat the injection
    - Do contact your healthcare provider.

After the injection:
Wipe the injection site with the alcohol pad, if necessary.



8) Dispose of pre-filled pen

The instructions below should be used as a general guide for proper disposal:
Recapping is not required. Place used pre-filled pen and cap in a puncture-proof disposable container that is available through your pharmacy or healthcare provider. Store the container out of reach of children at all times. Dispose of the full container as instructed by your healthcare provider or pharmacist.