ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

peginterferon alfa-2a*.....135 micrograms
Per vial of 1 ml of solution
* recombinant interferon alfa-2a produced by genetic engineering from *Escherichia coli* conjugated to bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear and colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pegasys is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see 4.4).

The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.

4.2 Posology and method of administration

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

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

Dose to be administered

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

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 regardless of viral load should receive 48 weeks of therapy.

Patients infected with HCV genotype 2/3 regardless of viral load should receive 24 weeks of therapy (see Table 1).

Table 1. Dosing Recommendations for Combination Therapy for HCV patients

Genotype	Pegasys Dose	Ribavirin Dose	Duration
Genotype 1	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotype 2/3	180 micrograms	800 mg	24 weeks

In general, patients infected with genotype 4 are considered hard to treat and limited study data (N=66) are compatible with a posology as for genotype 1. When deciding on the duration of therapy, the presence of additional risk factors should also be considered. For patients infected with genotype 5 or 6, this posology should also be considered.

The recommended duration of Pegasys monotherapy is 48 weeks.

HIV-HCV Co-infection
The recommended dosage for Pegasys, alone or in combination with 800 milligrams of ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with ribavirin doses greater than 800 milligrams daily or a duration of therapy less than 48 weeks has not been studied.

Predictability of response and non-response
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 8).

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.

Dose adjustment for adverse reactions

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. However, 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 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

Haematological (see also Table 3)
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.

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 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 apply: (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. As with other alpha interferons, increases in ALT levels above baseline (BL) have been observed in patients treated with Pegasys, including patients with a virological response. In clinical trials, 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 increase in ALT levels is progressive despite dose reduction, or is accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see 4.4 Special warnings and special precautions for use).

Special populations

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

Patients under the age of 18 years
The safety and efficacy of Pegasys have not been established in this population.

Patients with renal impairment
In patients with end stage renal disease, a starting dose of 135 micrograms should be used (see 5.2 Pharmacokinetic properties). 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.

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

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)

4.3 Contraindications

- Hypersensitivity to the active substance, to alpha interferons, or to any of the excipients
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see 4.4 Special warnings and special precautions for use)
- Pregnancy and lactation

- Initiation of Pegasys is contraindicated in HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6

For contraindications to ribavirin, please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

4.4 Special warnings and special precautions for use

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie, patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV genotype, age, extrahepatic manifestations, risk of transmission, etc. which influence the decision to treat or not.

In patients co-infected with HIV-HCV, limited efficacy and safety data (N = 51) are available in subjects with CD4 counts less than 200 cells/uL. Caution is therefore warranted in the treatment of patients with low CD4 counts.

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.

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 4.8 Undesirable effects). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see 4.2 Posology and method of administration).

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

The occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 15% of 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 4.8 Undesirable effects, Table 4). The risk of developing anaemia is higher in the female population.

As with other interferons, caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

Endocrine System
Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alpha 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 medication. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see 4.8 Undesirable effects). As with other interferons, hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Pegasys (see 4.8 Undesirable effects).

Psychiatric and Central Nervous System (CNS)
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.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during interferon or peginterferon alfa therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with interferon or peginterferon alfa. If patients develop psychiatric or CNS problems when treated with Pegasys, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue Pegasys therapy (see 4.8 Undesirable effects).

Cardiovascular system
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alpha 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 4.2 Posology and method of administration).

Liver function
In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. As with other alpha interferons, 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 4.2 Posology and method of administration and 4.8 Undesirable effects).

Hypersensitivity
Serious, acute hypersensitivity reaction (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If this occurs, therapy must be discontinued and appropriate medical therapy instituted immediately**.** Transient rashes do not necessitate interruption of treatment.

Autoimmune disease
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also 4.4 *Endocrine System* and 4.8 Undesirable effects).

Fever
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.

Ocular changes
As with other interferons retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction which may result in loss of vision have been reported in rare instances with 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. Patients with preexisting ophthalmologic disorders (eg, 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
As with other alpha interferons, 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 alpha interferons has been rarely 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 treatment have not been established in patients with liver transplantation.

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 SPC).

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).

Co-infected patients should be closely monitored, assessing their Child-Pugh score during treatment, and should be immediately discontinued if they progress to a Child-Pugh score of 7 or greater.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Results from a pharmacokinetic substudy of a pivotal phase III trial demonstrated no pharmacokinetic interaction between Pegasys and ribavirin.

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 hyperlactatemia/lactic acidosis have been reported with use of ribavirin.

4.6 Pregnancy and lactation

There are no adequate data on the use of peginterferon alfa-2a in pregnant women. Studies in animals with interferon alfa-2a have shown reproductive toxicity (see 5.3 Preclinical safety data) and the potential risk for humans is unknown. Pegasys should not be used during pregnancy.

Patients on treatment with Pegasys should take effective contraceptive measures.

It is not known whether peginterferon alfa-2a or any of the excipients of Pegasys are excreted in human milk. To avoid any potential for serious adverse reactions in nursing infants from Pegasys, a decision should be made whether to continue breast-feeding or to initiate Pegasys therapy, based on the importance of Pegasys therapy to the mother.

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 ribavirin. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded.

Please refer to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin (especially see 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.6 Pregnancy in the ribavirin SPC).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who develop dizziness, confusion, somnolence or fatigue should be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Experience from clinical trials

The frequency and severity of the most commonly reported adverse reactions with Pegasys are similar to those reported with interferon alfa-2a. 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.

HIV-HCV co-infected patients
In HIV-HCV co-infected patients, the clinical adverse event profiles reported for Pegasys, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients (see Tables 4 and 5). 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 viremia during therapy or follow-up. Limited safety data (N= 31) are available in co-infected patients with CD4+ cell counts <200/µl.

Table 4 summarises the safety overview of different treatment regimens of Pegasys in combination with ribavirin for HCV and HIV-HCV patients.

Table 4. Safety overview of Pegasys Treatment Regimens-Combination Therapy with Ribavirin for HCV and HIV-HCV patients

	HCV mono-infection **Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	**HCV mono-infection** **Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**HIV-HCV co-infection** **Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks
Serious adverse events	3%	11%	17%
Anemia (haemoglobin < 10g/dl)	3%	15%	14%
Ribavirin dose modification	19%	39%	37%
Premature withdrawals due to adverse events	4%	10%	12%
Premature withdrawals due to laboratory abnormalities	1%	3%	3%

Table 5 Undesirable Effects (≥ 10% Incidence in Any Treatment Group)

Body System	**HCV Pegasys** 180 mcg 48 weeks N=827	**HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks N=207	**HCV Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks N=887	**HCV IFN alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg 48 weeks N=443	**HIV-HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks N=288
	%	%	%	%	%
Metabolism & Nutrition					
Anorexia	16	20	27	26	23
Weight Decrease	5	2	7	10	16
Neuro/Psych Disorders					
Headache	52	48	47	49	35
Insomnia	20	30	32	37	19
Irritability	17	28	24	27	15
Depression	18	17	21	28	22
Dizziness	14	13	15	14	7
Concentration Impairment	9	8	10	13	2
Anxiety	6	8	8	12	8
Respiratory Disorder					
Dyspnoea	5	11	13	14	7
Cough	4	8	13	7	3
Gastrointestinal Disorders					
Nausea	24	29	28	28	24
Diarrhoea	16	15	14	10	16
Abdominal Pain	15	9	10	9	7
Skin					
Alopecia	22	25	24	33	10
Pruritus	12	25	21	18	5
Dermatitis	9	15	16	13	1
Dry skin	5	13	12	13	4
Musculoskeletal					
Myalgia	37	42	38	49	32
Arthralgia	26	20	22	23	16
General					
Fatigue	49	45	49	53	40
Pyrexia	35	37	39	54	41
Rigors	30	30	25	34	16
Injection-Site Reaction	22	28	21	15	10
Asthenia	7	18	15	16	26
Pain	11	9	10	9	6

Table 6. Undesirable Effects (<10% Incidence) Reported on Pegasys Monotherapy or In Combination with Ribavirin

Body system	Common <10% - 5%	Common <5% -1%	Uncommon to Rare serious adverse events <1% - <0.1%
Infections and infestations		herpes simplex, URI infection, bronchitis, oral candidiasis	skin infection, pneumonia,, otitis externa, endocarditis
Neoplasms benign and malignant			hepatic neoplasm
Blood and lymphatic system disorders		anaemia, lymphadenopathy, thrombocytopenia	
Immune system disorders			ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE, sarcoidosis, anaphylaxis
Endocrine disorders		hypothyroidism, hyperthyroidism	diabetes
Psychiatric disorders	mood alteration, emotional disorders	nervousness, libido decreased, aggression,	suicidal ideation,suicide,
Nervous system disorders	memory impairment	taste disturbance, weakness, paraesthesia, hypoaesthesia, tremor, migraine, somnolence, hyperaesthesia, nightmares, syncope	peripheral neuropathy, coma
Eye disorders		vision blurred, eye inflammation, xerophthalmia, eye pain	corneal ulcer, retinopathy, retinal vascular disorder, retinal hemorrhage, papilledema, optic neuropathy, vision loss
Ear and labyrinth disorders		vertigo, earache	
Cardiac disorders		palpitations, oedema peripheral, tachycardia	arrhythmia, supraventricular tachycardia, atrial fibrillation, CHF, angina, pericarditis, myocardial infarction
Vascular disorders		flushing	cerebral hemorrhage, hypertension
Respiratory, thoracic and mediastinal disorders		sore throat, dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, rhinitis, nasal congestion	wheezing, interstitial pneumonitis with fatal outcome, pulmonary embolism
Gastrointestinal disorders	vomiting, dry mouth, dyspepsia	mouth ulceration, flatulence, gingival bleeding, stomatitis, dysphagia, glossitis	peptic ulcer, gastrointestinal bleeding, reversible pancreactic reaction (ie, amylase/lipase increase with or without abdominal pain)
Hepato-biliary disorders			hepatic failure, hepatic dysfunction, fatty liver, cholangitis
Skin and subcutaneous tissue disorders	rash, sweating increased	eczema, night sweats, psoriasis, photosensitivity reaction, urticaria, skin disorder	angioedema
Musculoskeletal, connective tissue and bone disorders	back pain	muscle cramps, neck pain, musculoskeletal pain, bone pain, arthritis, muscle weakness	myositis
Reproductive system and breast disorders		impotence	
General disorders and administration site conditions		malaise, lethargy, chest pain, hot flushes, thirst, influenza like illness	
Injury and poisoning			substance overdose

Very rarely, alpha interferons including Pegasys, used alone or in combination with ribavirin, may be associated with pancytopenia including aplastic anemia.

For HIV-HCV patients receiving Pegasys and ribavirin combination therapy other undesirable effects have been reported in ≥ 1% to ≤ 2% of patients: hyperlactacidemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

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 4.4. Special warnings and special precautions for use). 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 (leukopenia, neutropenia, lymphopenia, thrombocytopenia and hemoglobin), which generally improved with dose modification, and returned to pre-treatment levels within 4-8 weeks upon cessation of therapy (see 4.2 Posology and method of administration and 4.4 Special warnings and special precautions for use).

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: however this was not correlated with lack of therapeutic response.

Thyroid function
Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see 4.4 Special warnings and special precautions for use). 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 hematological toxicities of neutropenia, thrombocytopenia and anemia 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. Anemia (hemoglobin < 10g/dL) was reported in 7% and 14% of patients treated with Pegasys monotherapy or in combination therapy, respectively.

4.9 Overdose

Overdoses involving between two injections on consecutive days (instead of weekly interval) up to daily injections for1 week (ie, 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: Immunostimulating Agent/Cytokine, ATC code: L03A B11

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.

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 trial results

Predictability of response
Please refer to section 4.2 Posology and method of administration, 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
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 9). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl. Clinical trials in non-responders and in relapsers are in progress.

For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see Tables 7, 8 and Table 9, 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 7 Virological Response

	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 patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and viral load are summarised in Tables 8 and 9 for HCV monoinfected patients and HIV-HCV co-infected patients, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype (see Table 1).

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

Table 8. Sustained Virological Response based on Genotype and Viral Load after Pegasys Combination Therapy with ribavirin

	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)*	41% (102/250)*	**52%** (142/271)*	45% (134/298)	36% (103/285)
Low viral load	41% (21/51)	52% (37/71)	55% (33/60)	**65%** (55/85)	53% (61/115)	44% (41/94)
High viral load	16% (8/50)	26% (12/47)	36% (69/190)	**47%** (87/186)	40% (73/182)	33% (62/189)
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)

* 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.

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.

HIV-HCV co-infected patients

Table 9. Sustained Virological Response based on Genotype and 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	7% (12/171)	14% (24/175)	29% (51/176)
Low viral load	19% (8/42)	38% (17/45)	61% (28/46)
High viral load	3% (4/129)	5% (7/130)	18% (23/130)
Genotype 2-3	20% (18/89)	36% (32/90)	62% (59/95)
Low viral load	27% (8/30)	38% (9/24)	61% (17/28)
High viral load	17% (10/59)	35% (23/66)	63% (42/67)

* Pegasys 180 mcg ribavirin 800mg vs. Interferon alfa-2a 3MIU ribavirin 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Pegasys 180 mcg ribavirin 800mg vs. Pegasys 180µg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Interferon alfa-2a 3MIU ribavirin 800mg vs. Pegasys 180mcg: Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), …P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomized 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.

5.2 Pharmacokinetic properties

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.

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 liters 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.

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. 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 is approximately 60 to 80 hours compared to values of 3-4 hours for standard interferon. The terminal half-life after subcutaneous administration is longer [50 to 130 hours]. The terminal half-life may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

Dose-proportional increases in exposure of Pegasys are seen in healthy subjects and in patients with chronic hepatitis C after once-weekly dosing.

In chronic hepatitis 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
Renal impairment is associated with slightly decreased CL/F and prolonged half-life. In patients (n=3) with CL_{crea} between 20 and 40 ml/min, the average CL/F is reduced by 25% compared with patients with normal renal function. In patients with end stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance, and doses of 135 micrograms result in similar exposure as 180 micrograms doses in patients with normal renal function (see 4.2 Posology and method of administration).

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

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 4.2 Posology and method of administration).

Hepatic impairment
The pharmacokinetics of Pegasys were similar between healthy subjects and patients with hepatitis 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 preclinical 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 alpha 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 anemia, 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, Pegasys 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.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

1 ml of solution for injection in vial (siliconised Type I glass) with stopper (rubber butyl). Available in packs of 1 or 4.

6.6 Instructions for use and handling, and disposal

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire, AL7 3AY
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/221/001
EU/1/02/221/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

peginterferon alfa-2a*.....180 micrograms
Per vial of 1 ml of solution
* recombinant interferon alfa-2a produced by genetic engineering from *Escherichia coli* conjugated to bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear and colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pegasys is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see 4.4).

The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.

4.2 Posology and method of administration

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

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

Dose to be administered

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

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 regardless of viral load should receive 48 weeks of therapy.

Patients infected with HCV genotype 2/3 regardless of viral load should receive 24 weeks of therapy(see Table 1).

Table 1. Dosing Recommendations for Combination Therapy for HCV patients

Genotype	Pegasys Dose	Ribavirin Dose	Duration
Genotype 1	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotype 2/3	180 micrograms	800 mg	24 weeks

In general, patients infected with genotype 4 are considered hard to treat and limited study data (N=66) are compatible with a posology as for genotype 1. When deciding on the duration of therapy, the presence of additional risk factors should also be considered. For patients infected with genotype 5 or 6, this posology should also be considered.

The recommended duration of Pegasys monotherapy is 48 weeks.

HIV-HCV Co-infection
The recommended dosage for Pegasys, alone or in combination with 800 milligrams of ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with ribavirin doses greater than 800 milligrams daily or a duration of therapy less than 48 weeks has not been studied.

Predictability of response and non-response
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 8).

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.

Dose adjustment for adverse reactions

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. However, 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 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

Haematological (see also Table 3)
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.

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 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 apply: (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. As with other alpha interferons, increases in ALT levels above baseline (BL) have been observed in patients treated with Pegasys, including patients with a virological response. In clinical trials, 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 to135 micrograms. When increase in ALT levels is progressive despite dose reduction, or is accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see 4.4 Special warnings and special precautions for use).

Special populations

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

Patients under the age of 18 years
The safety and efficacy of Pegasys have not been established in this population.

Patients with renal impairment
In patients with end stage renal disease, a starting dose of 135 micrograms should be used (see 5.2 Pharmacokinetic properties). 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.

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

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)

4.3 Contraindications

- Hypersensitivity to the active substance, to alpha interferons, or to any of the excipients
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see 4.4 Special warnings and special precautions for use)
- Pregnancy and lactation

- Initiation of Pegasys is contraindicated in HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6

For contraindications to ribavirin, please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

4.4 Special warnings and special precautions for use

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie, patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV genotype, age, extrahepatic manifestations, risk of transmission, etc. which influence the decision to treat or not.

In patients co-infected with HIV-HCV, limited efficacy and safety data (N = 51) are available in subjects with CD4 counts less than 200 cells/uL. Caution is therefore warranted in the treatment of patients with low CD4 counts.

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.

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 4.8 Undesirable effects). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see 4.2 Posology and method of administration).

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

The occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 15% of 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 4.8 Undesirable effects, Table 4). The risk of developing anaemia is higher in the female population.

As with other interferons, caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

Endocrine System
Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alpha 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 medication. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see 4.8 Undesirable effects). As with other interferons, hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Pegasys (see 4.8 Undesirable effects).

Psychiatric and Central Nervous System (CNS)
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.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during interferon or peginterferon alfa therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with interferon or peginterferon alfa. If patients develop psychiatric or CNS problems when treated with Pegasys, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue Pegasys therapy (see 4.8 Undesirable effects).

Cardiovascular system
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alpha 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 4.2 Posology and method of administration).

Liver function
In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. As with other alpha interferons, 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 4.2 Posology and method of administration and 4.8 Undesirable effects).

Hypersensitivity
Serious, acute hypersensitivity reaction (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If this occurs, therapy must be discontinued and appropriate medical therapy instituted immediately**.** Transient rashes do not necessitate interruption of treatment.

Autoimmune disease
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also 4.4 *Endocrine System* and 4.8 Undesirable effects).

Fever
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.

Ocular changes
As with other interferons retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction which may result in loss of vision have been reported in rare instances with 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. Patients with preexisting ophthalmologic disorders (eg, 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
As with other alpha interferons, 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 alpha interferons has been rarely 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 treatment have not been established in patients with liver transplantation.

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 SPC).

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).

Co-infected patients should be closely monitored, assessing their Child-Pugh score during treatment, and should be immediately discontinued if they progress to a Child-Pugh score of 7 or greater.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Results from a pharmacokinetic substudy of a pivotal phase III trial demonstrated no pharmacokinetic interaction between Pegasys and ribavirin.

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 hyperlactatemia/lactic acidosis have been reported with use of ribavirin.

4.6 Pregnancy and lactation

There are no adequate data on the use of peginterferon alfa-2a in pregnant women. Studies in animals with interferon alfa-2a have shown reproductive toxicity (see **5.3** Preclinical safety data) and the potential risk for humans is unknown. Pegasys should not be used during pregnancy.

Patients on treatment with Pegasys should take effective contraceptive measures.

It is not known whether peginterferon alfa-2a or any of the excipients of Pegasys are excreted in human milk. To avoid any potential for serious adverse reactions in nursing infants from Pegasys, a decision should be made whether to continue breast-feeding or to initiate Pegasys therapy, based on the importance of Pegasys therapy to the mother.

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 ribavirin. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded.

Please refer to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin (especially see 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.6 Pregnancy in the ribavirin SPC).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who develop dizziness, confusion, somnolence or fatigue should be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Experience from clinical trials

The frequency and severity of the most commonly reported adverse reactions with Pegasys are similar to those reported with interferon alfa-2a. 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.

HIV-HCV co-infected patients
In HIV-HCV co-infected patients, the clinical adverse event profiles reported for Pegasys, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients (see Tables 4 and 5). 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 viremia during therapy or follow-up. Limited safety data (N= 31) are available in co-infected patients with CD4+ cell counts <200/µl.

Table 4 summarises the safety overview of different treatment regimens of Pegasys in combination with ribavirin for HCV and HIV-HCV patients.

Table 4. Safety overview of Pegasys Treatment Regimens-Combination Therapy with Ribavirin for HCV and HIV-HCV patients

	HCV mono-infection **Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	**HCV mono-infection** **Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**HIV-HCV co-infection** **Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks
Serious adverse events	3%	11%	17%
Anemia (haemoglobin < 10g/dl)	3%	15%	14%
Ribavirin dose modification	19%	39%	37%
Premature withdrawals due to adverse events	4%	10%	12%
Premature withdrawals due to laboratory abnormalities	1%	3%	3%

Table 5 Undesirable Effects (≥ 10% Incidence in Any Treatment Group)

Body System	**HCV Pegasys** 180 mcg 48 weeks N=827	**HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks N=207	**HCV Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks N=887	**HCV IFN alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg 48 weeks N=443	**HIV-HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks N=288
	%	%	%	%	%
Metabolism & Nutrition					
Anorexia	16	20	27	26	23
Weight Decrease	5	2	7	10	16
Neuro/Psych Disorders					
Headache	52	48	47	49	35
Insomnia	20	30	32	37	19
Irritability	17	28	24	27	15
Depression	18	17	21	28	22
Dizziness	14	13	15	14	7
Concentration Impairment	9	8	10	13	2
Anxiety	6	8	8	12	8
Respiratory Disorder					
Dyspnoea	5	11	13	14	7
Cough	4	8	13	7	3
Gastrointestinal Disorders					
Nausea	24	29	28	28	24
Diarrhoea	16	15	14	10	16
Abdominal Pain	15	9	10	9	7
Skin					
Alopecia	22	25	24	33	10
Pruritus	12	25	21	18	5
Dermatitis	9	15	16	13	1
Dry skin	5	13	12	13	4
Musculoskeletal					
Myalgia	37	42	38	49	32
Arthralgia	26	20	22	23	16
General					
Fatigue	49	45	49	53	40
Pyrexia	35	37	39	54	41
Rigors	30	30	25	34	16
Injection-Site Reaction	22	28	21	15	10
Asthenia	7	18	15	16	26
Pain	11	9	10	9	6

Table 6. Undesirable Effects (<10% Incidence) Reported on Pegasys Monotherapy or In Combination with Ribavirin

Body system	Common <10% - 5%	Common <5% -1%	Uncommon to Rare serious adverse events <1% - <0.1%
Infections and infestations		herpes simplex, URI infection, bronchitis, oral candidiasis	skin infection, pneumonia,, otitis externa, endocarditis
Neoplasms benign and malignant			hepatic neoplasm
Blood and lymphatic system disorders		anaemia, lymphadenopathy, thrombocytopenia	
Immune system disorders			ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE, sarcoidosis, anaphylaxis
Endocrine disorders		hypothyroidism, hyperthyroidism	diabetes
Psychiatric disorders	mood alteration, emotional disorders	nervousness, libido decreased, aggression,	suicidal ideation,suicide,
Nervous system disorders	memory impairment	taste disturbance, weakness, paraesthesia, hypoaesthesia, tremor, migraine, somnolence, hyperaesthesia, nightmares, syncope	peripheral neuropathy, coma
Eye disorders		vision blurred, eye inflammation, xerophthalmia, eye pain	corneal ulcer, retinopathy, retinal vascular disorder, retinal hemorrhage, papilledema, optic neuropathy, vision loss
Ear and labyrinth disorders		vertigo, earache	
Cardiac disorders		palpitations, oedema peripheral, tachycardia	arrhythmia, supraventricular tachycardia, atrial fibrillation, CHF, angina, pericarditis, myocardial infarction
Vascular disorders		flushing	cerebral hemorrhage, hypertension
Respiratory, thoracic and mediastinal disorders		sore throat, dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, rhinitis, nasal congestion	wheezing, interstitial pneumonitis with fatal outcome, pulmonary embolism
Gastrointestinal disorders	vomiting, dry mouth, dyspepsia	mouth ulceration, flatulence, gingival bleeding, stomatitis, dysphagia, glossitis	peptic ulcer, gastrointestinal bleeding, reversible pancreactic reaction (ie, amylase/lipase increase with or without abdominal pain)
Hepato-biliary disorders			hepatic failure, hepatic dysfunction, fatty liver, cholangitis
Skin and subcutaneous tissue disorders	rash, sweating increased	eczema, night sweats, psoriasis, photosensitivity reaction, urticaria, skin disorder	angioedema
Musculoskeletal, connective tissue and bone disorders	back pain	muscle cramps, neck pain, musculoskeletal pain, bone pain, arthritis, muscle weakness	myositis
Reproductive system and breast disorders		impotence	
General disorders and administration site conditions		malaise, lethargy, chest pain, hot flushes, thirst, influenza like illness	
Injury and poisoning			substance overdose

Very rarely, alpha interferons including Pegasys, used alone or in combination with ribavirin, may be associated with pancytopenia including aplastic anemia.

For HIV-HCV patients receiving Pegasys and ribavirin combination therapy other undesirable effects have been reported in ≥ 1% to ≤ 2% of patients: hyperlactacidemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

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 4.4. Special warnings and special precautions for use). 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 (leukopenia, neutropenia, lymphopenia, thrombocytopenia and hemoglobin), which generally improved with dose modification, and returned to pre-treatment levels within 4-8 weeks upon cessation of therapy (see 4.2 Posology and method of administration and 4.4 Special warnings and special precautions for use).

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: however this was not correlated with lack of therapeutic response.

Thyroid function
Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see 4.4 Special warnings and special precautions for use). 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 hematological toxicities of neutropenia, thrombocytopenia and anemia 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. Anemia (hemoglobin < 10g/dL) was reported in 7% and 14% of patients treated with Pegasys monotherapy or in combination therapy, respectively.

4.9 Overdose

Overdoses involving between two injections on consecutive days (instead of weekly interval) up to daily injections for 1 week (ie, 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: Immunostimulating Agent/Cytokine, ATC code: L03A B11

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.

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 trial results

Predictability of response
Please refer to section 4.2 Posology and method of administration, 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
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 9). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl. Clinical trials in non-responders and in relapsers are in progress.

For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see Tables 7, 8 and Table 9, 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 7 Virological Response

	Pegasys Monotherapy				**Pegasys Combination Therapy**		
	non-cirrhotic and cirrhotic		**cirrhotic**		**non-cirrhotic and cirrhotic**		
	Study NV15496 + NV15497 + NV 15801		**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 patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and viral load are summarised in Tables 8 and 9 for HCV monoinfected patients and HIV-HCV co-infected patients, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype (see Table 1).

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

Table 8. Sustained Virological Response based on Genotype and Viral Load after Pegasys Combination Therapy with ribavirin

	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)*	41% (102/250)*	**52%** (142/271)*	45% (134/298)	36% (103/285)
Low viral load	41% (21/51)	52% (37/71)	55% (33/60)	**65%** (55/85)	53% (61/115)	44% (41/94)
High viral load	16% (8/50)	26% (12/47)	36% (69/190)	**47%** (87/186)	40% (73/182)	33% (62/189)
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)

* 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.

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.

HIV-HCV co-infected patients

Table 9. Sustained Virological Response based on Genotype and 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	7% (12/171)	14% (24/175)	29% (51/176)
Low viral load	19% (8/42)	38% (17/45)	61% (28/46)
High viral load	3% (4/129)	5% (7/130)	18% (23/130)
Genotype 2-3	20% (18/89)	36% (32/90)	62% (59/95)
Low viral load	27% (8/30)	38% (9/24)	61% (17/28)
High viral load	17% (10/59)	35% (23/66)	63% (42/67)

* Pegasys 180 mcg ribavirin 800mg vs. Interferon alfa-2a 3MIU ribavirin 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Pegasys 180 mcg ribavirin 800mg vs. Pegasys 180µg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Interferon alfa-2a 3MIU ribavirin 800mg vs. Pegasys 180mcg: Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), …P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomized 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.

5.2 Pharmacokinetic properties

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.

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 liters 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.

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. 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 is approximately 60 to 80 hours compared to values of 3-4 hours for standard interferon. The terminal half-life after subcutaneous administration is longer [50 to 130 hours]. The terminal half-life may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

Dose-proportional increases in exposure of Pegasys are seen in healthy subjects and in patients with chronic hepatitis C after once-weekly dosing.

In chronic hepatitis 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
Renal impairment is associated with slightly decreased CL/F and prolonged half-life. In patients (n=3) with CL_{crea} between 20 and 40 ml/min, the average CL/F is reduced by 25% compared with patients with normal renal function. In patients with end stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance, and doses of 135 micrograms result in similar exposure as 180 micrograms doses in patients with normal renal function (see 4.2 Posology and method of administration).

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

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 4.2 Posology and method of administration).

Hepatic impairment
The pharmacokinetics of Pegasys were similar between healthy subjects and patients with hepatitis 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 preclinical 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 alpha 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 anemia, 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, Pegasys 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.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

1 ml of solution for injection in vial (siliconised Type I glass) with stopper (rubber butyl). Available in packs of 1 or 4.

6.6 Instructions for use and handling, and disposal

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire, AL7 3AY
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/221/003
EU/1/02/221/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains
peginterferon alfa-2a*.....135 micrograms
in 0.5 ml of solution

* recombinant interferon alfa-2a produced by genetic engineering from *Escherichia coli* conjugated to bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

The solution is clear and colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pegasys is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see 4.4).

The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.

4.2 Posology and method of administration

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

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

Dose to be administered

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 s given in Table 1.
The ribavirin dose should be administered with food.

Duration of treatment

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 regardless of viral load should receive 48 weeks of therapy. Patients infected with HCV genotype 2/3 regardless of viral load should receive 24 weeks of therapy(see Table 1).

Table 1. Dosing Recommendations for Combination therapy for HCV patients

Genotype	Pegasys Dose	Ribavirin Dose	Duration
Genotype 1	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotype 2/3	180 micrograms	800 mg	24 weeks

In general, patients infected with genotype 4 are considered hard to treat and limited study data (N=66) are compatible with a posology as for genotype 1. When deciding on the duration of therapy, the presence of additional risk factors should also be considered. For patients infected with genotype 5 or 6, this posology should also be considered.

The recommended duration of Pegasys monotherapy is 48 weeks.

HIV-HCV Co-infection
The recommended dosage for Pegasys, alone or in combination with 800 milligrams of ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with ribavirin doses greater than 800 milligrams daily or a duration of therapy less than 48 weeks has not been studied.

Predictability of response and non-response
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 8).

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.

Dose adjustment for adverse reactions

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. However, 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 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

Haematological (see also Table3)
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.

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 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 apply: (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. As with other alpha interferons, increases in ALT levels above baseline (BL) have been observed in patients treated with Pegasys, including patients with a virological response. In clinical trials, 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 increase in ALT levels is progressive despite dose reduction, or is accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see 4.4 Special warnings and special precautions for use).

Special populations

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

Patients under the age of 18 years
The safety and efficacy of Pegasys have not been established in this population.

Patients with renal impairment
In patients with end stage renal disease, a starting dose of 135 micrograms should be used (see 5.2 Pharmacokinetic properties). 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.

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

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)

4.3 Contraindications

- Hypersensitivity to the active substance, to alpha interferons, or to any of the excipients
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see 4.4 Special warnings and special precautions for use)
- Pregnancy and lactation

- Initiation of Pegasys is contraindicated in HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6

For contraindications to ribavirin, please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

4.4 Special warnings and special precautions for use

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie, patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV genotype, age, extrahepatic manifestations, risk of transmission, etc. which influence the decision to treat or not.

In patients co-infected with HIV-HCV, limited efficacy and safety data (N = 51) are available in subjects with CD4 counts less than 200 cells/uL. Caution is therefore warranted in the treatment of patients with low CD4 counts.

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.

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 4.8 Undesirable effects). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see 4.2 Posology and method of administration).

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

The occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 15% of 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 4.8 Undesirable effects, Table 4). The risk of developing anaemia is higher in the female population.

As with other interferons, caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

Endocrine System
Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alpha 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 medication. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see 4.8 Undesirable effects). As with other interferons, hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Pegasys (see 4.8 Undesirable effects).

Psychiatric and Central Nervous System (CNS)
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.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during interferon or peginterferon alfa therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with interferon or peginterferon alfa. If patients develop psychiatric or CNS problems when treated with Pegasys, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue Pegasys therapy (see 4.8 Undesirable effects).

Cardiovascular system
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alpha 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 4.2 Posology and method of administration).

Liver function
In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. As with other alpha interferons, 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 4.2 Posology and method of administration and 4.8 Undesirable effects).

Hypersensitivity
Serious, acute hypersensitivity reaction (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If this occurs, therapy must be discontinued and appropriate medical therapy instituted immediately**.** Transient rashes do not necessitate interruption of treatment.

Autoimmune disease
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also 4.4 *Endocrine System* and 4.8 Undesirable effects).

Fever
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.

Ocular changes
As with other interferons retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction which may result in loss of vision have been reported in rare instances with 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. Patients with preexisting ophthalmologic disorders (eg, 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
As with other alpha interferons, 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 alpha interferons has been rarely 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 treatment have not been established in patients with liver transplantation.

HIV-HCV co-infected patients
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 SPC).

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).

Co-infected patients should be closely monitored, assessing their Child-Pugh score during treatment, and should be immediately discontinued if they progress to a Child-Pugh score of 7 or greater.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Results from a pharmacokinetic substudy of a pivotal phase III trial demonstrated no pharmacokinetic interaction between Pegasys and ribavirin.

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 hyperlactatemia/lactic acidosis have been reported with use of ribavirin.

4.6 Pregnancy and lactation

There are no adequate data on the use of peginterferon alfa-2a in pregnant women. Studies in animals with interferon alfa-2a have shown reproductive toxicity (see **5.3** Preclinical safety data) and the potential risk for humans is unknown. Pegasys should not be used during pregnancy.

Patients on treatment with Pegasys should take effective contraceptive measures.

It is not known whether peginterferon alfa-2a or any of the excipients of Pegasys are excreted in human milk. To avoid any potential for serious adverse reactions in nursing infants from Pegasys, a decision should be made whether to continue breast-feeding or to initiate Pegasys therapy, based on the importance of Pegasys therapy to the mother.

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 ribavirin. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded.

Please refer to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin (especially see 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.6 Pregnancy in the ribavirin SPC).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who develop dizziness, confusion, somnolence or fatigue should be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Experience from clinical trials

The frequency and severity of the most commonly reported adverse reactions with Pegasys are similar to those reported with interferon alfa-2a.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.

HIV-HCV co-infected patients
In HIV-HCV co-infected patients, the clinical adverse event profiles reported for Pegasys, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients (see Tables 4 and 5). 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 viremia during therapy or follow-up. Limited safety data (N= 31) are available in co-infected patients with CD4+ cell counts <200/µl.

Table 4 summarises the safety overview of different treatment regimens of Pegasys in combination with ribavirin for HCV and HIV-HCV patients.

Table 4. Safety overview of Pegasys Treatment Regimens-Combination Therapy with Ribavirin for HCV and HIV-HCV patients

	HCV mono-infection **Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	**HCV mono-infection** **Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**HIV-HCV co-infection** **Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks
Serious adverse events	3%	11%	17%
Anemia (haemoglobin < 10g/dl)	3%	15%	14%
Ribavirin dose modification	19%	39%	37%
Premature withdrawals due to adverse events	4%	10%	12%
Premature withdrawals due to laboratory abnormalities	1%	3%	3%

Table 5 Undesirable Effects (≥ 10% Incidence in Any Treatment Group)

Body System	**HCV Pegasys** 180 mcg 48 weeks N=827	**HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks N=207	**HCV Pegasys** 180 mcg & **Ribavirin 1000/1200 mg** 48 weeks N=887	**HCV IFN alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg 48 weeks N=443	**HIV-HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks N=288
	%	%	%	%	%
Metabolism & Nutrition					
Anorexia	16	20	27	26	23
Weight Decrease	5	2	7	10	16
Neuro/Psych Disorders					
Headache	52	48	47	49	35
Insomnia	20	30	32	37	19
Irritability	17	28	24	27	15
Depression	18	17	21	28	22
Dizziness	14	13	15	14	7
Concentration Impairment	9	8	10	13	2
Anxiety	6	8	8	12	8
Respiratory Disorder					
Dyspnoea	5	11	13	14	7
Cough	4	8	13	7	3
Gastrointestinal Disorders					
Nausea	24	29	28	28	24
Diarrhoea	16	15	14	10	16
Abdominal Pain	15	9	10	9	7
Skin					
Alopecia	22	25	24	33	10
Pruritus	12	25	21	18	5
Dermatitis	9	15	16	13	1
Dry skin	5	13	12	13	4
Musculoskeletal					
Myalgia	37	42	38	49	32
Arthralgia	26	20	22	23	16
General					
Fatigue	49	45	49	53	40
Pyrexia	35	37	39	54	41
Rigors	30	30	25	34	16
Injection-Site Reaction	22	28	21	15	10
Asthenia	7	18	15	16	26
Pain	11	9	10	9	6

Table 6. Undesirable Effects (<10% Incidence) Reported on Pegasys Monotherapy or In Combination with Ribavirin

Body system	Common <10% - 5%	Common <5% -1%	Uncommon to Rare serious adverse events <1% - <0.1%
Infections and infestations		herpes simplex, URI infection, bronchitis, oral candidiasis	skin infection, pneumonia,, otitis externa, endocarditis
Neoplasms benign and malignant			hepatic neoplasm
Blood and lymphatic system disorders		anaemia, lymphadenopathy, thrombocytopenia	
Immune system disorders			ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE , sarcoidosis, anaphylaxis
Endocrine disorders		hypothyroidism, hyperthyroidism	diabetes
Psychiatric disorders	mood alteration, emotional disorders	nervousness, libido decreased, aggression,	suicidal ideation, suicide,
Nervous system disorders	memory impairment	taste disturbance, weakness, paraesthesia, hypoaesthesia, tremor, migraine, somnolence, hyperaesthesia, nightmares, syncope	peripheral neuropathy, coma
Eye disorders		vision blurred, eye inflammation, xerophthalmia, eye pain	corneal ulcer, retinopathy, retinal vascular disorder, retinal hemorrhage, papilledema, optic neuropathy, vision loss
Ear and labyrinth disorders		vertigo, earache	
Cardiac disorders		palpitations, oedema peripheral, tachycardia	arrhythmia, supraventricular tachycardia, atrial fibrillation, CHF, angina, pericarditis, myocardial infarction
Vascular disorders		flushing	cerebral hemorrhage, hypertension
Respiratory, thoracic and mediastinal disorders		sore throat, dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, rhinitis, nasal congestion	wheezing, interstitial pneumonitis with fatal outcome, pulmonary embolism
Gastrointestinal disorders	vomiting, dry mouth, dyspepsia	mouth ulceration, flatulence, gingival bleeding, stomatitis, dysphagia, glossitis	peptic ulcer, gastrointestinal bleeding, reversible pancreactic reaction (ie, amylase/lipase increase with or without abdominal pain)
Hepato-biliary disorders			hepatic failure, hepatic dysfunction, fatty liver, cholangitis
Skin and subcutaneous tissue disorders	rash, sweating increased	eczema, night sweats, psoriasis, photosensitivity reaction, urticaria, skin disorder	angioedema
Musculoskeletal, connective tissue and bone disorders	back pain	muscle cramps, neck pain, musculoskeletal pain, bone pain, arthritis, muscle weakness	myositis
Reproductive system and breast disorders		impotence	
General disorders and administration site conditions		malaise, lethargy, chest pain, hot flushes, thirst, influenza like illness	
Injury and poisoning			substance overdose

Very rarely, alpha interferons including Pegasys, used alone or in combination with ribavirin, may be associated with pancytopenia including aplastic anemia.

For HIV-HCV patients receiving Pegasys and ribavirin combination therapy other undesirable effects have been reported in ≥ 1% to ≤ 2% of patients: hyperlactacidemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

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 4.4. Special warnings and special precautions for use). 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 (leukopenia, neutropenia, lymphopenia, thrombocytopenia and hemoglobin), which generally improved with dose modification, and returned to pre-treatment levels within 4-8 weeks upon cessation of therapy (see 4.2 Posology and method of administration and 4.4 Special warnings and special precautions for use).

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: however this was not correlated with lack of therapeutic response.

Thyroid function
Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see 4.4 Special warnings and special precautions for use). 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 hematological toxicities of neutropenia, thrombocytopenia and anemia 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. Anemia (hemoglobin < 10g/dL) was reported in 7% and 14% of patients treated with Pegasys monotherapy or in combination therapy, respectively.

4.9 Overdose

Overdoses involving between two injections on consecutive days (instead of weekly interval) up to daily injections for 1 week (ie, 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: Immunostimulating Agent/Cytokine, ATC code: L03A B11

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.

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 is followed by and 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 trial results

Predictability of response
Please refer to section 4.2 Posology and method of administration, 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
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 9). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl. Clinical trials in non-responders and in relapsers are in progress.

For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see Tables 7, 8 and Table 9, 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 7 Virological Response

	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 patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and viral load are summarised in Tables 8 and 9 for HCV monoinfected patients and HIV-HCV co-infected patients, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype (see Table 1).

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

Table 8. Sustained Virological Response based on Genotype and Viral Load after Pegasys Combination Therapy with ribavirin

	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)*	41% (102/250)*	**52%** (142/271)*	45% (134/298)	36% (103/285)
Low viral load	41% (21/51)	52% (37/71)	55% (33/60)	**65%** (55/85)	53% (61/115)	44% (41/94)
High viral load	16% (8/50)	26% (12/47)	36% (69/190)	**47%** (87/186)	40% (73/182)	33% (62/189)
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)

* 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.

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.

HIV-HCV co-infected patients

Table 9. Sustained Virological Response based on Genotype and 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	7% (12/171)	14% (24/175)	29% (51/176)
Low viral load	19% (8/42)	38% (17/45)	61% (28/46)
High viral load	3% (4/129)	5% (7/130)	18% (23/130)
Genotype 2-3	20% (18/89)	36% (32/90)	62% (59/95)
Low viral load	27% (8/30)	38% (9/24)	61% (17/28)
High viral load	17% (10/59)	35% (23/66)	63% (42/67)

* Pegasys 180 mcg ribavirin 800mg vs. Interferon alfa-2a 3MIU ribavirin 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Pegasys 180 mcg ribavirin 800mg vs. Pegasys 180µg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Interferon alfa-2a 3MIU ribavirin 800mg vs. Pegasys 180mcg: Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), …P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomized 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.

5.2 Pharmacokinetic properties

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.

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 liters 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.

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. 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 is approximately 60 to 80 hours compared to values of 3-4 hours for standard interferon. The terminal half-life after subcutaneous administration is longer [50 to 130 hours]. The terminal half-life may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

Dose-proportional increases in exposure of Pegasys are seen in healthy subjects and in patients with chronic hepatitis C after once-weekly dosing.

In chronic hepatitis 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
Renal impairment is associated with slightly decreased CL/F and prolonged half-life. In patients (n=3) with CL_{crea} between 20 and 40 ml/min, the average CL/F is reduced by 25% compared with patients with normal renal function. In patients with end stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance, and doses of 135 micrograms result in similar exposure as 180 micrograms doses in patients with normal renal function (see 4.2 Posology and method of administration).

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

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 4.2 Posology and method of administration).

Hepatic impairment
The pharmacokinetics of Pegasys were similar between healthy subjects and patients with hepatitis 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 preclinical 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 alpha 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 anemia, 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, Pegasys 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.
Store in the original package 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. Available in packs of 1, 4 or 12.

6.6 Instructions for use and handling, and disposal

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire, AL7 3AY
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/221/005
EU/1/02/221/006
EU/1/02/221/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Pegasys 180 micrograms solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains
peginterferon alfa-2a*.....180 micrograms
in 0.5 ml of solution

* recombinant interferon alfa-2a produced by genetic engineering from *Escherichia coli* conjugated to bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

The solution is clear and colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pegasys is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see 4.4).

The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.

4.2 Posology and method of administration

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

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

Dose to be administered

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

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 regardless of viral load should receive 48 weeks of therapy. Patients infected with HCV genotype 2/3 regardless of viral load should receive 24 weeks of therapy(see Table1).

Table 1. Dosing Recommendations for Combination Therapy for HCV patients

Genotype	Pegasys Dose	Ribavirin Dose	Duration
Genotype 1	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotype 2/3	180 micrograms	800 mg	24 weeks

In general, patients infected with genotype 4 are considered hard to treat and limited study data (N=66) are compatible with a posology as for genotype 1. When deciding on the duration of therapy, the presence of additional risk factors should also be considered. For patients infected with genotype 5 or 6, this posology should also be considered.

The recommended duration of Pegasys monotherapy is 48 weeks.

HIV-HCV Co-infection
The recommended dosage for Pegasys, alone or in combination with 800 milligrams of ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks, regardless of genotype. The safety and efficacy of combination therapy with ribavirin doses greater than 800 milligrams daily or a duration of therapy less than 48 weeks has not been studied.

Predictability of response and non-response
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 8).

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.

Dose adjustment for adverse reactions

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. However, 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 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects).

Haematological (see also Table 3)
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.

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 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 apply: (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. As with other alpha interferons, increases in ALT levels above baseline (BL) have been observed in patients treated with Pegasys, including patients with a virological response. In clinical trials, 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 increase in ALT levels is progressive despite dose reduction, or is accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see 4.4 Special warnings and special precautions for use).

Special populations

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

Patients under the age of 18 years
The safety and efficacy of Pegasys have not been established in this population.

Patients with renal impairment
In patients with end stage renal disease, a starting dose of 135 micrograms should be used (see 5.2 Pharmacokinetics properties). 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.

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

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)

4.3 Contraindications

- Hypersensitivity to the active substance, to alpha interferons, or to any of the excipients
- Autoimmune hepatitis
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see 4.4 Special warnings and special precautions for use)
- Pregnancy and lactation

- Initiation of Pegasys is contraindicated in HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6

For contraindications to ribavirin, please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

4.4 Special warnings and special precautions for use

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (ie, patients with genotype 2 or 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

In patients with normal ALT, progression of fibrosis occurs on average at a slower rate than in patients with elevated ALT. This should be considered in conjunction with other factors, such as HCV genotype, age, extrahepatic manifestations, risk of transmission, etc. which influence the decision to treat or not.

In patients co-infected with HIV-HCV, limited efficacy and safety data (N = 51) are available in subjects with CD4 counts less than 200 cells/uL. Caution is therefore warranted in the treatment of patients with low CD4 counts.

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 4weeks and biochemical tests should be performed at 4weeks. Additional testing should be performed periodically during therapy.

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 4.8 Undesirable effects). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see 4.2 Posology and method of administration).

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

The occurrence of anaemia (haemoglobin <10 g/dl) has been observed in up to 15% of 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 4.8 Undesirable effects, Table 4). The risk of developing anaemia is higher in the female population.

As with other interferons, caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

Endocrine System
Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alpha 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 medication. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see 4.8 Undesirable effects). As with other interferons, hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Pegasys (see 4.8 Undesirable effects).

Psychiatric and Central Nervous System (CNS)
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.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during interferon or peginterferon alfa therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with interferon or peginterferon alfa. If patients develop psychiatric or CNS problems when treated with Pegasys, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue Pegasys therapy (see 4.8 Undesirable effects).

Cardiovascular system
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alpha 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 4.2 Posology and method of administration).

Liver function
In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. As with other alpha interferons, 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 4.2 Posology and method of administration and 4.8 Undesirable effects).

Hypersensitivity
Serious, acute hypersensitivity reaction (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If this occurs, therapy must be discontinued and appropriate medical therapy instituted immediately. Transient rashes do not necessitate interruption of treatment.

Autoimmune disease
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also 4.4 *Endocrine System* and 4.8 Undesirable effects).

Fever
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.

Ocular changes
As with other interferons retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction which may result in loss of vision have been reported in rare instances with 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. Patients with preexisting ophthalmologic disorders (eg, 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
As with other alpha interferons, 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 alpha interferons has been rarely 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 treatment have not been established in patients with liver transplantation.

HIV/HCV co-infected patients
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 SPC).

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).

Co-infected patients should be closely monitored, assessing their Child-Pugh score during treatment, and should be immediately discontinued if they progress to a Child-Pugh score of 7 or greater.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Results from a pharmacokinetic substudy of a pivotal phase III trial demonstrated no pharmacokinetic interaction between Pegasys and ribavirin.

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 hyperlactatemia/lactic acidosis have been reported with use of ribavirin.

4.6 Pregnancy and lactation

There are no adequate data on the use of peginterferon alfa-2a in pregnant women. Studies in animals with interferon alfa-2a have shown reproductive toxicity (see **5.3** Preclinical safety data) and the potential risk for humans is unknown. Pegasys should not be used during pregnancy.

Patients on treatment with Pegasys should take effective contraceptive measures.

It is not known whether peginterferon alfa-2a or any of the excipients of Pegasys are excreted in human milk. To avoid any potential for serious adverse reactions in nursing infants from Pegasys, a decision should be made whether to continue breast-feeding or to initiate Pegasys therapy, based on the importance of Pegasys therapy to the mother.

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 ribavirin. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded.

Please refer to the ribavirin Summary of Product Characteristics (SPC) when Pegasys is to be used in combination with ribavirin (especially see 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.6 Pregnancy in the ribavirin SPC).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who develop dizziness, confusion, somnolence or fatigue should be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Experience from clinical trials

The frequency and severity of the most commonly reported adverse reactions with Pegasys are similar to those reported with interferon alfa-2a. 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.

HIV-HCV co-infected patients
In HIV-HCV co-infected patients, the clinical adverse event profiles reported for Pegasys, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients (see Tables 4 and 5). 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 viremia during therapy or follow-up. Limited safety data (N= 31) are available in co-infected patients with CD4+ cell counts <200/µl.

Table 4 summarises the safety overview of different treatment regimens of Pegasys in combination with ribavirin for HCV and HIV-HCV patients.

Table 4. Safety overview of Pegasys Treatment Regimens-Combination Therapy with Ribavirin for HCV and HIV-HCV patients

	HCV mono-infection **Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks	**HCV mono-infection** **Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks	**HIV-HCV co-infection** **Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks
Serious adverse events	3%	11%	17%
Anemia (haemoglobin < 10g/dl)	3%	15%	14%
Ribavirin dose modification	19%	39%	37%
Premature withdrawals due to adverse events	4%	10%	12%
Premature withdrawals due to laboratory abnormalities	1%	3%	3%

Table 5 Undesirable Effects (≥ 10% Incidence in Any Treatment Group)

Body System	**HCV Pegasys** 180 mcg 48 weeks N=827	**HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks N=207	**HCV Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks N=887	**HCV IFN alfa-2b** 3 MIU & **Ribavirin** 1000/1200 mg 48 weeks N=443	**HIV-HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks N=288
	%	%	%	%	%
Metabolism & Nutrition					
Anorexia	16	20	27	26	23
Weight Decrease	5	2	7	10	16
Neuro/Psych Disorders					
Headache	52	48	47	49	35
Insomnia	20	30	32	37	19
Irritability	17	28	24	27	15
Depression	18	17	21	28	22
Dizziness	14	13	15	14	7
Concentration Impairment	9	8	10	13	2
Anxiety	6	8	8	12	8
Respiratory Disorder					
Dyspnoea	5	11	13	14	7
Cough	4	8	13	7	3
Gastrointestinal Disorders					
Nausea	24	29	28	28	24
Diarrhoea	16	15	14	10	16
Abdominal Pain	15	9	10	9	7
Skin					
Alopecia	22	25	24	33	10
Pruritus	12	25	21	18	5
Dermatitis	9	15	16	13	1
Dry skin	5	13	12	13	4
Musculoskeletal					
Myalgia	37	42	38	49	32
Arthralgia	26	20	22	23	16
General					
Fatigue	49	45	49	53	40
Pyrexia	35	37	39	54	41
Rigors	30	30	25	34	16
Injection-Site Reaction	22	28	21	15	10
Asthenia	7	18	15	16	26
Pain	11	9	10	9	6

Table 6. Undesirable Effects (<10% Incidence) Reported on Pegasys Monotherapy or In Combination with Ribavirin

Body system	Common <10% - 5%	Common <5% -1%	Uncommon to Rare serious adverse events <1% - <0.1%
Infections and infestations		herpes simplex, URI infection, bronchitis, oral candidiasis	skin infection, pneumonia,, otitis externa, endocarditis
Neoplasms benign and malignant			hepatic neoplasm
Blood and lymphatic system disorders		anaemia, lymphadenopathy, thrombocytopenia	
Immune system disorders			ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE, sarcoidosis, anaphylaxis
Endocrine disorders		hypothyroidism, hyperthyroidism	diabetes
Psychiatric disorders	mood alteration, emotional disorders	nervousness, libido decreased, aggression,	suicidal ideation,suicide,
Nervous system disorders	memory impairment	taste disturbance, weakness, paraesthesia, hypoaesthesia, tremor, migraine, somnolence, hyperaesthesia, nightmares, syncope	peripheral neuropathy, coma
Eye disorders		vision blurred, eye inflammation, xerophthalmia, eye pain	corneal ulcer, retinopathy, retinal vascular disorder, retinal hemorrhage, papilledema, optic neuropathy, vision loss
Ear and labyrinth disorders		vertigo, earache	
Cardiac disorders		palpitations, oedema peripheral, tachycardia	arrhythmia, supraventricular tachycardia, atrial fibrillation, CHF, angina, pericarditis, myocardial infarction
Vascular disorders		flushing	cerebral hemorrhage, hypertension
Respiratory, thoracic and mediastinal disorders		sore throat, dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, rhinitis, nasal congestion	wheezing, interstitial pneumonitis with fatal outcome, pulmonary embolism
Gastrointestinal disorders	vomiting, dry mouth, dyspepsia	mouth ulceration, flatulence, gingival bleeding, stomatitis, dysphagia, glossitis	peptic ulcer, gastrointestinal bleeding, reversible pancreactic reaction (ie, amylase/lipase increase with or without abdominal pain)
Hepato-biliary disorders			hepatic failure, hepatic dysfunction, fatty liver, cholangitis
Skin and subcutaneous tissue disorders	rash, sweating increased	eczema, night sweats, psoriasis, photosensitivity reaction, urticaria, skin disorder	angioedema
Musculoskeletal, connective tissue and bone disorders	back pain	muscle cramps, neck pain, musculoskeletal pain, bone pain, arthritis, muscle weakness	myositis
Reproductive system and breast disorders		impotence	
General disorders and administration site conditions		malaise, lethargy, chest pain, hot flushes, thirst, influenza like illness	
Injury and poisoning			substance overdose

Very rarely, alpha interferons including Pegasys, used alone or in combination with ribavirin, may be associated with pancytopenia including aplastic anemia.

For HIV-HCV patients receiving Pegasys and ribavirin combination therapy other undesirable effects have been reported in ≥ 1% to ≤ 2% of patients: hyperlactacidemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

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 4.4. Special warnings and special precautions for use). 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 (leukopenia, neutropenia, lymphopenia, thrombocytopenia and hemoglobin), which generally improved with dose modification, and returned to pre-treatment levels within 4-8 weeks upon cessation of therapy (see 4.2 Posology and method of administration and 4.4 Special warnings and special precautions for use).

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: however this was not correlated with lack of therapeutic response.

Thyroid function
Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see 4.4 Special warnings and special precautions for use). 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 hematological toxicities of neutropenia, thrombocytopenia and anemia 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/mm3 was observed in 13% and 11% of patients receiving Pegasys monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm3 was observed in 10% and 8% of patients receiving Pegasys monotherapy and combination therapy, respectively. Anemia (hemoglobin < 10g/dL) was reported in 7% and 14% of patients treated with Pegasys monotherapy or in combination therapy, respectively.

4.9 Overdose

Overdoses involving between two injections on consecutive days (instead of weekly interval) up to daily injections for 1 week (ie, 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: Immunostimulating Agent/Cytokine, ATC code: L03A B11

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.

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 trial results

Predictability of response
Please refer to section 4.2 Posology and method of administration, 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
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 9). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl. Clinical trials in non-responders and in relapsers are in progress.

For HCV monoinfected patients and HIV-HCV co-infected patients , for treatment regimens, duration of therapy and study outcome see Tables 7, 8 and Table 9, 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 7 Virological Response

	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 patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and viral load are summarised in Tables 8 and 9 for HCV monoinfected patients and HIV-HCV co-infected patients, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype (see Table 1).

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

Table 8. Sustained Virological Response based on Genotype and Viral Load after Pegasys Combination Therapy with ribavirin

	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)*	41% (102/250)*	**52%** (142/271)*	45% (134/298)	36% (103/285)
Low viral load	41% (21/51)	52% (37/71)	55% (33/60)	**65%** (55/85)	53% (61/115)	44% (41/94)
High viral load	16% (8/50)	26% (12/47)	36% (69/190)	**47%** (87/186)	40% (73/182)	33% (62/189)
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)

* 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.

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.

HIV-HCV co-infected patients

Table 9. Sustained Virological Response based on Genotype and 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	7% (12/171)	14% (24/175)	29% (51/176)
Low viral load	19% (8/42)	38% (17/45)	61% (28/46)
High viral load	3% (4/129)	5% (7/130)	18% (23/130)
Genotype 2-3	20% (18/89)	36% (32/90)	62% (59/95)
Low viral load	27% (8/30)	38% (9/24)	61% (17/28)
High viral load	17% (10/59)	35% (23/66)	63% (42/67)

* Pegasys 180 mcg ribavirin 800mg vs. Interferon alfa-2a 3MIU ribavirin 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Pegasys 180 mcg ribavirin 800mg vs. Pegasys 180µg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Interferon alfa-2a 3MIU ribavirin 800mg vs. Pegasys 180mcg: Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), …P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

HCV patients with normal ALT
In study NR16071, HCV patients with normal ALT values were randomized 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.

5.2 Pharmacokinetic properties

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.

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 liters 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.

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. 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 is approximately 60 to 80 hours compared to values of 3-4 hours for standard interferon. The terminal half-life after subcutaneous administration is longer [50 to 130 hours]. The terminal half-life may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

Dose-proportional increases in exposure of Pegasys are seen in healthy subjects and in patients with chronic hepatitis C after once-weekly dosing.

In chronic hepatitis 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
Renal impairment is associated with slightly decreased CL/F and prolonged half-life. In patients (n=3) with CL_{crea} between 20 and 40 ml/min, the average CL/F is reduced by 25% compared with patients with normal renal function. In patients with end stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance, and doses of 135 micrograms result in similar exposure as 180 micrograms doses in patients with normal renal function (see 4.2 Posology and method of administration).

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

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 4.2 Posology and method of administration).

Hepatic impairment
The pharmacokinetics of Pegasys were similar between healthy subjects and patients with hepatitis 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 preclinical 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 alpha 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 anemia, 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, Pegasys 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.
Store in the original package 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. Available in packs of 1, 4 or 12.

6.6 Instructions for use and handling, and disposal

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire, AL7 3AY
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/221/007
EU/1/02/221/008
EU/1/02/221/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110
USA

Roche Diagnostics GmbH
Nonnenwald 2
D-82377 Penzberg
Germany

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE 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)

1 vial contains 135 micrograms of peginterferon alfa -2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial
135 micrograms in 1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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
40 Broadwater Road
Welwyn Garden City
Hertfordshire, AL7 3AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/001

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE 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)

1 vial contains 135 micrograms of peginterferon alfa-2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials
135 micrograms in 1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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
40 Broadwater Road
Welwyn Garden City
Hertfordshire, AL7 3AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/002

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGLE DOSE 135 µg VIAL

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

Pegasys 135 micrograms solution for injection
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

135 µg in 1ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE 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)

1 vial contains 180 micrograms of peginterferon alfa-2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial
180 micrograms in 1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/003

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE 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)

1 vial contains 180 micrograms of peginterferon alfa-2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials
180 micrograms in 1 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/004

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGLE DOSE 180 µg VIAL

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

Pegasys 180 micrograms solution for injection
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

180 µg in 1 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE 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)

1 pre-filled syringe contains 135 micrograms of peginterferon alfa –2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe + 1 injection needle
135 micrograms in 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/005

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE 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)

1 pre-filled syringe contains 135 micrograms of peginterferon alfa –2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

4 pre-filled syringes + 4 injection needles
135 micrograms in 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/006

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON – 12 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)

1 pre-filled syringe contains 135 micrograms of peginterferon alfa –2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

12 pre-filled syringes + 12 injection needles
135 micrograms in 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/009

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

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 micrograms solution for injection
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

135 µg in 0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE 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)

1 pre-filled syringe contains 180 micrograms of peginterferon alfa -2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe + 1 injection needle
180 micrograms in 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/007

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON – 4 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)

1 pre-filled syringe contains 180 micrograms of peginterferon alfa –2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

4 pre-filled syringes + 4 injection needles
180 micrograms in 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/008

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON – 12 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)

1 pre-filled syringe contains 180 micrograms of peginterferon alfa –2a

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

12 pre-filled syringes + 12 injection needles
180 micrograms in 0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

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

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Store in the original package 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

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/221/010

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

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 micrograms solution for injection
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

180 µg in 0.5 ml

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Pegasys 135 micrograms solution for injection
Peginterferon alfa-2a

- The active substance is peginterferon alfa-2a (conjugation of recombinant interferon alfa-2a with bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000), 135 micrograms in a single dose vial.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections.

Marketing Authorisation Holder

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Manufacturer

Hoffmann-La Roche AG
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D-79639 Grenzach-Wyhlen
Germany

1. WHAT PEGASYS IS AND WHAT IT IS USED FOR

Pegasys is presented as a solution for injection in a vial (1 ml) available in packs containing 1 or 4 single dose vials.

Pegasys 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 for the treatment of chronic hepatitis C, which is a viral infection of the liver.

Pegasys is best used for this treatment in combination with ribavirin.
If you will receive combination therapy of Pegasys and ribavirin, you should also read the ribavirin package leaflet.
Pegasys is used alone only if you cannot take ribavirin for any reason.

2. 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 Pegasys.
- if you have ever had a heart attack or suffer from other heart disease.
- if you have, so called autoimmune hepatitis.
- if you have advanced liver disease (e.g. your skin has become yellow).
- if the patient is a child less than 3 years old.
- if you are pregnant or breast-feeding.

Take special care with Pegasys:
Tell your doctor:
- if you are planning on becoming pregnant, discuss this with your doctor before starting to use Pegasys (see Pregnancy).
- if you have psoriasis, it may get worse during treatment with Pegasys.
- if you have a problem with your liver other than hepatitis C.
- if you have diabetes or high blood pressure, your doctor may ask you to have an eye examination.
- if you notice a change in your vision.
- when receiving Pegasys, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection (such as pneumonia).
- if you develop symptoms associated with a cold or other respiratory infection (such as cough, fever or any difficulty in breathing).
- 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 have thyroid disease that is not well controlled with medicines.
- if you have had a severe nervous or mental disorder.
- if you have ever had depression or develop symptoms associated with depression while on treatment with Pegasys (e.g. feelings of sadness, dejection etc).
- if you have ever had anaemia.
- if you are coinfected with HIV and treated with anti HIV medicinal products.

Pregnancy:
Do not use Pegasys during pregnancy. When Pegasys is given in combination with ribavirin, it is important to avoid pregnancy for you (if you are a female patient) or your female partner (if you are a male patient) during treatment and during the 6 months after treatment. Ribavirin can be very harmful to the unborn child. Therefore, both you and your partner should use two forms of effective contraception during treatment and for six months after. Please follow the recommendation given by your doctor. Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding:
Do not breast-feed an infant if you are being treated with Pegasys. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
Do not drive or use machinery if you feel drowsy, tired, or confused while taking Pegasys.

Taking other medicines:
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. Please be sure to read the ribavirin Patient Leaflet also.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE PEGASYS

Always take Pegasys as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. Your doctor has prescribed Pegasys specifically for you and your current condition; do not share this medicine with anyone else.

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 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 6 months to 1 year depending on the type of virus you are infected with. 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 self-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 the case of combination therapy with Pegasys and ribavirin, please follow the dosing regimen recommended by your doctor.

- **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 forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pegasys can have side effects. Although not all of the unwanted effects may occur, they may need medical attention if they do. During treatment your doctor will take blood samples regularly to check for changes in your blood cells and in liver function.

Check with your doctor immediately if any of the following side effects occur: severe chest pain; persistent cough; irregular heartbeat; trouble breathing; confusion; depression; severe stomach pain; blood in stool or urine; severe nosebleed; fever or chills; problems with your eyesight.

Some people get depressed when taking Pegasys alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. 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 change in your behaviour.

The most common side effects with the combination of Pegasys and ribavirin are flu-like symptoms such as aches and pains, nausea, and diarrhoea; inability to sleep, loss of hair, irritability, injection site irritation and skin reactions.

Other common side effects are inability to concentrate, chest pain, muscle pain, nosebleeds, gum irritation, constipation, lip inflammation, weight loss, anxiety, poor memory, increased sweating, mood/emotion changes and back pain.

Less common side effects are dry mouth, mouth sores, numbness or tingling, decreased sexual desire, sleepiness, tremors, anemia, decreased platelets, palpitations, eye irritation, sinus congestion, airway infection, taste disturbance, flatulence and swollen glands.

When Pegasys is used alone, some of these effects are less likely to occur.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGASYS

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

Do not use after the expiry date stated on the label.

Do not use Pegasys if 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.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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HOW TO SELF INJECT PEGASYS

The following instructions explain how to use Pegasys single dose vials to inject yourself. 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

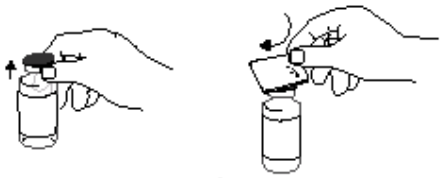
Wash your hand carefully before handling any of the items.

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**).

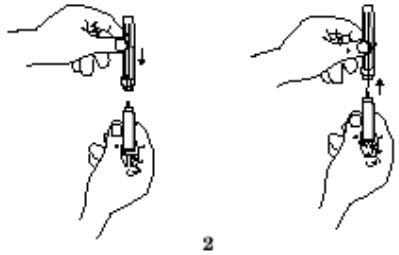


1

- Clean the rubber top of the vial with a cleansing swab.

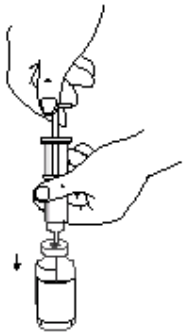
You can save the swab to clean the skin area where you will inject Pegasys.

- 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**).



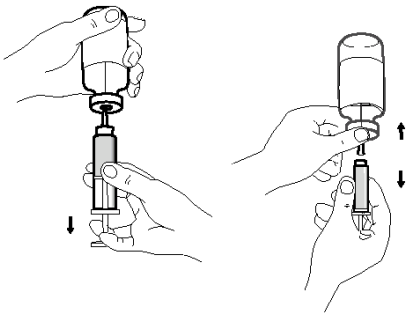
2

- 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

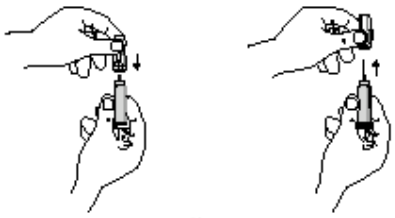
- Hold the vial and syringe in one hand and turn the vial and the syringe upside down (**4**).



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**).



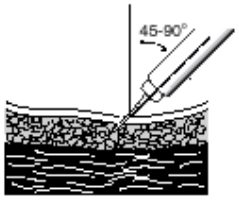
5

- 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 the 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

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Pegasys 180 micrograms solution for injection
Peginterferon alfa-2a

- The active substance is peginterferon alfa-2a (conjugation of recombinant interferon alfa-2a with bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000), 180 micrograms in a single dose vial.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections.

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Manufacturer

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Germany

1. WHAT PEGASYS IS AND WHAT IT IS USED FOR

Pegasys is presented as a solution for injection in a vial (1 ml) available in packs containing 1 or 4 single dose vials.

Pegasys 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 for the treatment of chronic hepatitis C, which is a viral infection of the liver.

Pegasys is best used for this treatment in combination with ribavirin.
If you receive combination therapy of Pegasys and ribavirin, you should also read the ribavirin package leaflet.
Pegasys is used alone only if you cannot take ribavirin for any reason.

2. 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 Pegasys.
- if you have ever had a heart attack or suffer from other heart disease.
- if you have, so called autoimmune hepatitis.
- if you have advanced liver disease (e.g. your skin has become yellow).
- if the patient is a child less than 3 years old.
- if you are pregnant or breast-feeding.

Take special care with Pegasys:
Tell your doctor:
- if you are planning on becoming pregnant, discuss this with your doctor before starting to use Pegasys (see Pregnancy).
- if you have psoriasis, it may get worse during treatment with Pegasys.
- if you have a problem with your liver other than hepatitis C.
- if you have diabetes or high blood pressure, your doctor may ask you to have an eye examination
- if you notice a change in your vision.
- when receiving Pegasys, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection (such as pneumonia).
- if you develop symptoms associated with a cold or other respiratory infection (such as cough, fever or any difficulty in breathing).
- 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 have thyroid disease that is not well controlled with medicines.
- if you have had a severe nervous or mental disorder.
- if you have ever had depression or develop symptoms associated with depression while on treatment with Pegasys (e.g. feelings of sadness, dejection etc).
- if you have ever had anaemia.
- if you are coinfected with HIV and treated with anti HIV medicinal products.

Pregnancy:
Do not use Pegasys during pregnancy. When Pegasys is given in combination with ribavirin, it is important to avoid pregnancy for you (if you are a female patient) or your female partner (if you are a male patient) during treatment and during the 6 months after treatment. Ribavirin can be very harmful to the unborn child. Therefore, both you and your partner should use two forms of effective contraception during treatment and for six months after. Please follow the recommendation given by your doctor. Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding:
Do not breast-feed an infant if you are being treated with Pegasys. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
Do not drive or use machinery if you feel drowsy, tired, or confused while taking Pegasys.

Taking other medicines:
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. Please be sure to read the ribavirin Patient Leaflet also.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE PEGASYS

Always take Pegasys as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. Your doctor has prescribed Pegasys specifically for you and your current condition; do not share this medicine with anyone else.

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 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 6 months to 1 year depending on the type of virus you are infected with. 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 self-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 the case of combination therapy with Pegasys and ribavirin, please follow the dosing regimen recommended by your doctor.

- **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 forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pegasys can have side effects. Although not all of the unwanted effects may occur, they may need medical attention if they do. During treatment your doctor will take blood samples regularly to check for changes in your blood cells and in liver function.

Check with your doctor immediately if any of the following side effects occur: severe chest pain; persistent cough; irregular heartbeat; trouble breathing; confusion; depression; severe stomach pain; blood in stool or urine; severe nosebleed; fever or chills; problems with your eyesight.

Some people get depressed when taking Pegasys alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. 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 change in your behaviour.

The most common side effects with the combination of Pegasys and ribavirin are flu-like symptoms such as aches and pains, nausea, and diarrhoea; inability to sleep, loss of hair, irritability, injection site irritation and skin reactions.

Other common side effects are inability to concentrate, chest pain, muscle pain, nosebleeds, gum irritation, constipation, lip inflammation, weight loss, anxiety, poor memory, increased sweating, mood/emotion changes and back pain.

Less common side effects are dry mouth, mouth sores, numbness or tingling, decreased sexual desire, sleepiness, tremors, anemia, decreased platelets, palpitations, eye irritation, sinus congestion, airway infection, taste disturbance, flatulence and swollen glands.

When Pegasys is used alone, some of these effects are less likely to occur.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGASYS

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

Do not use after the expiry date stated on the label.

Do not use Pegasys if 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.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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HOW TO SELF-INJECT PEGASYS

The following instructions explain how to use Pegasys single dose vials to inject yourself. 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

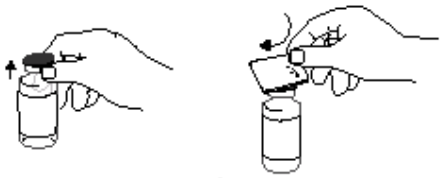
Wash your hand carefully before handling any of the items.

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**).

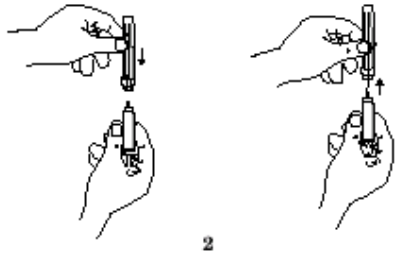


1

- Clean the rubber top of the vial with a cleansing swab.

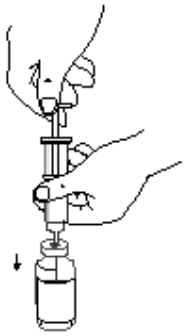
You can save the swab to clean the skin area where you will inject Pegasys.

- 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**).



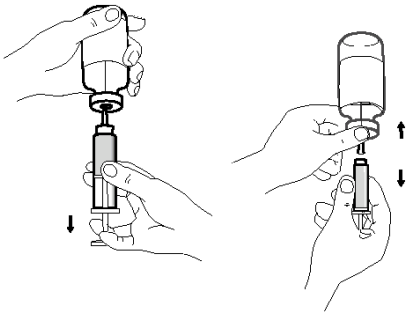
2

- 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

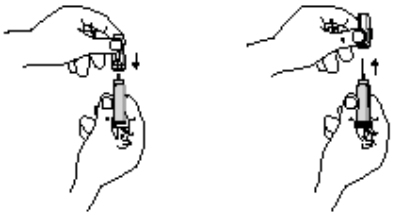
- Hold the vial and syringe in one hand and turn the vial and the syringe upside down (**4**).



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**).



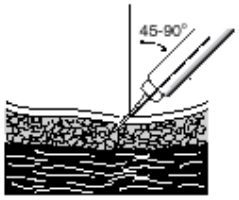
5

- 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 the 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

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

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

- The active substance is peginterferon alfa-2a (conjugation of recombinant interferon alfa-2a with bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000), 135 micrograms in a pre-filled syringe.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections.

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United Kingdom

Manufacturer

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

1. WHAT PEGASYS IS AND WHAT IT IS USED FOR

Pegasys is presented as a solution for injection in a pre-filled syringe (0.5 ml) with a separate injection needle available in packs containing 1, 4 or 12 pre-filled syringes.

Pegasys 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 for the treatment of chronic hepatitis C, which is a viral infection of the liver.

Pegasys is best used for this treatment in combination with ribavirin.
If you receive combination therapy of Pegasys and ribavirin, you should also read the ribavirin package leaflet.
Pegasys is used alone only if you cannot take ribavirin for any reason.

2. 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 Pegasys.
- if you have ever had a heart attack or suffer from other heart disease.
- if you have, so called autoimmune hepatitis.
- if you have advanced liver disease (e.g. your skin has become yellow).
- if the patient is a child less than 3 years old.
- if you are pregnant or breast-feeding.

Take special care with Pegasys:
Tell your doctor:
- if you are planning on becoming pregnant, discuss this with your doctor before starting to use Pegasys (see Pregnancy).
- if you have psoriasis, it may get worse during treatment with Pegasys.
- if you have a problem with your liver other than hepatitis C.
- if you have diabetes or high blood pressure, your doctor may ask you to have an eye examination.
- if you notice a change in your vision.
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- if you develop symptoms associated with a cold or other respiratory infection (such as cough, fever or any difficulty in breathing).
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- if you have thyroid disease that is not well controlled with medicines.
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- if you have ever had depression or develop symptoms associated with depression while on treatment with Pegasys (e.g. feelings of sadness, dejection etc).
- if you have ever had anaemia.
- if you are coinfected with HIV and treated with anti HIV medicinal products.

Pregnancy:
Do not use Pegasys during pregnancy. When Pegasys is given in combination with ribavirin, it is important to avoid pregnancy for you (if you are a female patient) or your female partner (if you are a male patient) during treatment and during the 6 months after treatment. Ribavirin can be very harmful to the unborn child. Therefore, both you and your partner should use two forms of effective contraception during treatment and for six months after. Please follow the recommendation given by your doctor. Ask your doctor or pharmacist for advice before taking any medicine.

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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 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 6 months to 1 year depending on the type of virus you are infected with. 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 self-inject Pegasys"**).

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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 the case of combination therapy with Pegasys and ribavirin, please follow the dosing regimen recommended by your doctor.

- **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.

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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 forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pegasys can have side effects. Although not all of the unwanted effects may occur, they may need medical attention if they do. During treatment your doctor will take blood samples regularly to check for changes in your blood cells and in liver function.

Check with your doctor immediately if any of the following side effects occur: severe chest pain; persistent cough; irregular heartbeat; trouble breathing; confusion; depression; severe stomach pain; blood in stool or urine; severe nosebleed; fever or chills; problems with your eyesight.

Some people get depressed when taking Pegasys alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. 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 change in your behaviour.

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Other common side effects are inability to concentrate, chest pain, muscle pain, nosebleeds, gum irritation, constipation, lip inflammation, weight loss, anxiety, poor memory, increased sweating, mood/emotion changes and back pain.

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When Pegasys is used alone, some of these effects are less likely to occur.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGASYS

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze.
Store in the original package in order to protect from light.

Do not use after the expiry date stated on the label.

Do not use Pegasys if 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.

6. FURTHER INFORMATION

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HOW TO SELF- INJECT PEGASYS

The following instructions explain how to use Pegasys pre-filled syringes to inject yourself. 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.

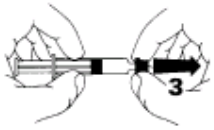
Collect the necessary items before beginning:
Included in the pack:
- a pre-filled syringe of Pegasys
- an injection needle

Not included in the pack:
- a cleansing swab
- small bandage or sterile gauze
- an adhesive bandage
- a container for the waste material

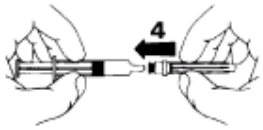
Preparing the syringe and needle for injection

- Remove the protective cap that covers the back of the needle (**1**-**2**).

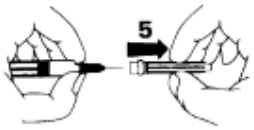
- Remove the rubber cap from the syringe (**3**). Do not touch the tip of the syringe.



- Place the needle firmly on the tip of the syringe (**4**).



- Remove the needle guard from the syringe needle (**5**).



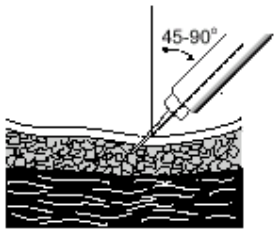
- To remove air bubbles from the syringe, hold the syringe with the needle pointing up. Tap the syringe gently to bring the bubbles to the top. Push the plunger up slowly to the correct dose. Replace the needle guard and place the syringe in a horizontal position until ready for use.
- Allow the solution 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 the 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**).



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- 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

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

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

- The active substance is peginterferon alfa-2a (conjugation of recombinant interferon alfa-2a with bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000), 180 micrograms in a pre-filled syringe.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid and water for injections.

Marketing Authorisation Holder

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United Kingdom

Manufacturer

Hoffmann-La Roche AG
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D-79639 Grenzach-Wyhlen
Germany

1. WHAT PEGASYS IS AND WHAT IT IS USED FOR

Pegasys is presented as a solution for injection in a pre-filled syringe (0.5 ml) with a separate injection needle available in packs containing 1, 4 or 12 pre-filled syringes.

Pegasys 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 for the treatment of chronic hepatitis C, which is a viral infection of the liver.

Pegasys is best used for this treatment in combination with ribavirin.
If you receive combination therapy of Pegasys and ribavirin, you should also read the ribavirin package leaflet.
Pegasys is used alone only if you cannot take ribavirin for any reason.

2. 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 Pegasys.
- if you have ever had a heart attack or suffer from other heart disease.
- if you have, so called autoimmune hepatitis.
- if you have advanced liver disease (e.g. your skin has become yellow).
- if the patient is a child less than 3 years old.
- if you are pregnant or breast-feeding.

Take special care with Pegasys:
Tell your doctor:
- if you are planning on becoming pregnant, discuss this with your doctor before starting to use Pegasys (see Pregnancy).
- if you have psoriasis, it may get worse during treatment with Pegasys.
- if you have a problem with your liver other than hepatitis C.
- if you have diabetes or high blood pressure, your doctor may ask you to have an eye examination.
- if you notice a change in your vision.
- when receiving Pegasys, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection (such as pneumonia).
- if you develop symptoms associated with a cold or other respiratory infection (such as cough, fever or any difficulty in breathing).
- 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 have thyroid disease that is not well controlled with medicines.
- if you have had a severe nervous or mental disorder.
- if you have ever had depression or develop symptoms associated with depression while on treatment with Pegasys (e.g. feelings of sadness, dejection etc).
- if you have ever had anaemia.
- if you are coinfected with HIV and treated with anti HIV medicinal products.

Pregnancy:
Do not use Pegasys during pregnancy. When Pegasys is given in combination with ribavirin, it is important to avoid pregnancy for you (if you are a female patient) or your female partner (if you are a male patient) during treatment and during the 6 months after treatment. Ribavirin can be very harmful to the unborn child. Therefore, both you and your partner should use two forms of effective contraception during treatment and for six months after. Please follow the recommendation given by your doctor. Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding:
Do not breast-feed an infant if you are being treated with Pegasys. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
Do not drive or use machinery if you feel drowsy, tired, or confused while taking Pegasys.

Taking other medicines:
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. Please be sure to read the ribavirin Patient Leaflet also.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

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Always take Pegasys as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. Your doctor has prescribed Pegasys specifically for you and your current condition; do not share this medicine with anyone else.

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 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 6 months to 1 year depending on the type of virus you are infected with . Please check with your doctor and follow the recommended duration of treatment.
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Combination therapy with ribavirin
In the case of combination therapy with Pegasys and ribavirin, please follow the dosing regimen recommended by your doctor.

- **If you use more Pegasys than you should:**

Contact your doctor or pharmacist as soon as possible.

- **If you forget to take Pegasys:**

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The following instructions explain how to use Pegasys pre-filled syringes to inject yourself. 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.

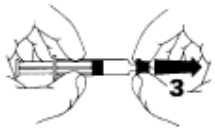
Collect the necessary items before beginning:
Included in the pack:
- a pre-filled syringe of Pegasys
- an injection needle

Not included in the pack:
- a cleansing swab
- small bandage or sterile gauze
- an adhesive bandage
- a container for the waste material

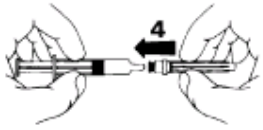
Preparing the syringe and needle for injection

- Remove the protective cap that covers the back of the needle (**1**-**2**).

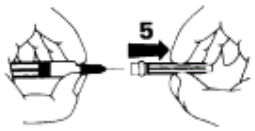
- Remove the rubber cap from the syringe (**3**). Do not touch the tip of the syringe.



- 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.
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- 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 the cleansing swab.
- Wait for the area to dry.
- Remove the needle guard.
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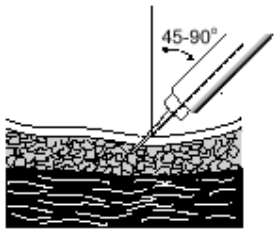
- Insert the needle all the way into the pinched skin at an angle of 45° to 90° (**6**).



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.