SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pegasys 135 micrograms solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pegasys 90 micrograms solution for injection in pre-filled syringe
Each syringe of 0.5 mL solution contains 90 micrograms peginterferon alfa-2a*.
Pegasys 135 micrograms solution for injection in pre-filled syringe
Each syringe of 0.5 mL solution contains 135 micrograms peginterferon alfa-2a*.
Pegasys 180 micrograms solution for injection in pre-filled syringe
Each syringe of 0.5 mL solution contains 180 micrograms peginterferon alfa-2a*.
The strength indicates the quantity of the interferon alfa-2a moiety of peginterferon alfa-2a without consideration of the pegylation.
*The active substance, peginterferon alfa-2a, is a covalent conjugate of the protein interferon alfa-2a produced by recombinant DNA technology in *Escherichia coli* with bis-[monomethoxy polyethylene glycol].
The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1.

Excipient with known effect:
Each pre-filled syringe of 0.5 mL contains 5 mg benzyl alcohol.
Each pre-filled syringe of 0.5 mL contains 0.025 mg polysorbate 80. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
The solution is clear and colourless to light yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Polycythaemia vera
Pegasys is indicated as monotherapy in adults for the treatment of polycythaemia vera.

Essential thrombocythaemia
Pegasys is indicated as monotherapy in adults for the treatment of essential thrombocythaemia.

Chronic hepatitis B
Adult patients
Pegasys is indicated for the treatment of hepatitis B envelope antigen (HBeAg)-positive or HBeAg-negative chronic hepatitis B (CHB) in adult patients with compensated liver disease and evidence of viral replication, increased alanine aminotransferase (ALT) and histologically verified liver inflammation and/or fibrosis (see sections 4.4 and 5.1).
Paediatric patients 3 years of age and older
Pegasys is indicated for the treatment of HBeAg-positive CHB in non-cirrhotic children and adolescents 3 years of age and older with evidence of viral replication and persistently elevated serum ALT levels. With respect to the decision to initiate treatment in paediatric patients see sections 4.2, 4.4 and 5.1.

Chronic hepatitis C
Adult patients
Pegasys is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC) in patients with compensated liver disease (see sections 4.2, 4.4 and 5.1).
For hepatitis C virus (HCV) genotype specific activity, see sections 4.2 and 5.1.
Paediatric patients 5 years of age and older
Pegasys in combination with ribavirin is indicated for the treatment of CHC in treatment-naïve children and adolescents 5 years of age and older who are positive for serum HCV-RNA.
When deciding to initiate treatment in childhood, it is important to consider growth inhibition induced by combination therapy. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

4.2 Posology and method of administration

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

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

Posology

Polycythemia vera and essential thrombocythemia – adult patients

The dose should be titrated individually with a recommended starting dose of 45 micrograms once weekly subcutaneously. The dose should be gradually increased by 45 micrograms monthly until stabilisation of the haematological parameters is achieved. The dose may be adapted and/or the administration interval prolonged, as appropriate for the patient.
For polycythemia vera a stabilisation of the haematological parameters is defined as haematocrit (HCT) <45% without phlebotomy and platelets $\leq 400 \times 10^9$/L and leukocytes $< 10 \times 10^9$/L.
For essential thrombocythemia the stabilisation of the haematological parameters is defined as platelets $\leq 400 \times 10^9$/L and leukocytes $< 10 \times 10^9$/L.
The maximum recommended single dose is 180 micrograms injected once weekly subcutaneously.
If adverse reactions develop during therapy, the administered dose should be reduced or treatment discontinued temporarily until adverse reactions abate; further, treatment should be re-initiated with a lower dose than the dose that caused adverse reactions (see section 4.4).
If an increase of haematological parameters (HCT, platelets, leukocytes) is observed, the dose and/or dosing interval needs to be adapted individually.

Chronic hepatitis B – adult patients

The recommended dosage and duration of Pegasys for both HBeAg-positive and HBeAg-negative CHB is 180 micrograms once weekly for 48 weeks. For information on predictive values for on-treatment response, see section 5.1.

Chronic hepatitis C – adult patients

Treatment-naïve adult patients

The recommended dose for Pegasys is 180 micrograms once weekly given in combination with oral ribavirin or as monotherapy.
The dose of ribavirin to be used in combination with Pegasys is given in Table 1.
The ribavirin dose should be administered with food.

Duration of treatment – dual therapy with Pegasys and ribavirin

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

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

who become HCV RNA negative at week 4 and remain HCV RNA negative at week 24. However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section

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

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

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

Table 1: Dosing recommendations for combination therapy for adult patients with chronic hepatitis C

Genotype	Pegasys dose	Ribavirin dose	Duration
Genotype 1 LVL with RVR*	180 micrograms	<75 kg = 1 000 mg ≥75 kg = 1 200 mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	180 micrograms	<75 kg = 1 000 mg ≥75 kg = 1 200 mg	48 weeks
Genotype 4 with RVR*	180 micrograms	<75 kg = 1 000 mg ≥75 kg = 1 200 mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	180 micrograms	<75 kg = 1 000 mg ≥75 kg = 1 200 mg	48 weeks
Genotype 2 or 3 without RVR**	180 micrograms	800 mg	24 weeks
Genotype 2 or 3 LVL with RVR**	180 micrograms	800 mg[(a)]	16 weeks[(a)] or 24 weeks
Genotype 2 or 3 HVL with RVR**	180 micrograms	800 mg	24 weeks

*RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24;

**RVR = rapid viral response (HCV RNA negative) by week 4
LVL = ≤ 800 000 IU/mL; HVL = > 800 000 IU/mL
[(a)] It is presently not clear whether a higher dose of ribavirin (e.g. 1 000/1 200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.

The ultimate clinical impact of a shortened initial treatment of 16 weeks instead of 24 weeks is unknown, taking into account the need for re-treating non-responding and relapsing patients.
The recommended duration of Pegasys monotherapy is 48 weeks.

Treatment-experienced adult patients
The recommended dose of Pegasys in combination with ribavirin is 180 micrograms once weekly by subcutaneous administration. For patients <75 kg and ≥75 kg, 1 000 mg daily and 1°200 mg daily of ribavirin, respectively, and regardless of genotype, should be administered.
Patients who have detectable virus at week 12 should stop therapy. The recommended total duration of therapy is 48 weeks. If patients infected with virus genotype 1, not responding to prior treatment with peginterferon and ribavirin are considered for treatment, the recommended total duration of therapy is 72 weeks (see section 5.1).

HIV-HCV co-infected adult patients
The recommended dosage for Pegasys, alone or in combination with ribavirin, is 180 micrograms once weekly subcutaneously for 48 weeks. For patients infected with HCV genotype 1 <75 kg and ≥75 kg, 1 000 mg daily and 1 200 mg daily of ribavirin, respectively, should be administered. Patients infected with HCV genotypes other than genotype 1 should receive 800 mg daily of ribavirin. A duration of therapy less than 48 weeks has not been adequately studied.
Duration of therapy when Pegasys is used in combination with other medicinal products
Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with Pegasys.

Predictability of response and non-response with Pegasys and ribavirin dual therapy – treatment-naïve patients
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (see Tables 2 and 14).

Table 2: Predictive value of week 12 virological response at the recommended dosing regimen while on Pegasys combination therapy in adult patients with chronic hepatitis C

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

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

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

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

Haematological (see also Table 3)
For adults, dose reduction is recommended if the absolute neutrophil count (ANC) is 500 to < 750 cells/mm^3. For patients with ANC < 500 cells/mm^3 treatment should be suspended until ANC values return to > 1 000 cells/mm^3. Therapy should initially be reinstituted at 90 micrograms Pegasys and the neutrophil count monitored.
Dose reduction to 90 micrograms is recommended if the platelet count is 25 000 to < 50 000 cells/mm^3. Treatment discontinuation is recommended when platelet count decreases to levels < 25 000 cells/mm^3.

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

Table 3: Dose adjustment for adverse reactions in adult patients (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			500 to < 750 cells/mm^3	< 500 cells/mm^3	
Platelet Count			25 000 to < 50 000 cells/mm^3		< 25 000 cells/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 CHC. Increases in ALT levels above baseline (BL) have been observed in patients treated with Pegasys, including patients with a virological response. In CHC clinical trials with adult patients, isolated increases in ALT (≥ 10x upper limit of normal [ULN], or ≥ 2x BL for patients with a BL ALT ≥ 10x ULN) which resolved without dose-modification were observed in 8 of 451 patients treated with combination therapy. If ALT increase is progressive or persistent, the dose should be reduced initially to 135 micrograms. When increases in ALT levels are progressive despite dose reduction, or are accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see section 4.4).

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

Chronic hepatitis B and C - paediatric patients
Pegasys is contraindicated in neonates and young children up to 3 years old due to the excipient benzyl alcohol (see sections 4.3 and 4.4).
Patients who initiate treatment prior to their 18th birthday should maintain paediatric dosing through the completion of therapy.
The posology of Pegasys in paediatric patients is based on the Body Surface Area (BSA). To calculate BSA, it is recommended to use Mosteller's equation:

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

The recommended duration of therapy is 48 weeks in patients with CHB. Before initiating therapy for CHB, persistently elevated serum ALT levels should have been documented. The response rate was lower in patients with no to minimal increase in ALT level at baseline (see section 5.1).

The duration of treatment with Pegasys in combination with ribavirin in paediatric patients with CHC depends on viral genotype. Patients infected with viral genotypes 2 or 3 should receive 24 weeks of treatment, while patients infected with any other genotype should receive 48 weeks of therapy. Patients who still have detectable levels of HCV-RNA despite an initial 24 weeks of therapy, should discontinue therapy, as it is unlikely, they will be able to achieve a sustained virological response with continued therapy.

For children and adolescents aged 3 to 17 years with CHB and having a BSA greater than 0.54 m^2 and for children and adolescents aged 5 to 17 years with CHC and having a BSA greater than 0.71 m^2, the recommended doses for Pegasys are provided in Table 4.

Table 4: Pegasys dosing recommendations for paediatric patients with chronic hepatitis B and chronic hepatitis C

Body Surface Area (BSA) range (m^2)		**Weekly dose (mcg)**
CHC	**CHB**	
0.71-0.74	0.54-0.74	65
0.75-1.08		90
1.09-1.51		135
>1.51		180

For paediatric patients, based on toxicities, up to three levels of dose modification can be made before dose interruption or discontinuation is considered (see Table 5).

Table 5: Pegasys dose modification recommendations in paediatric patients with chronic hepatitis B or chronic hepatitis C

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

Recommendations for dose modifications of Pegasys for toxicities in the CHB and CHC paediatric populations are presented in Table 6.

Table 6: Pegasys dose modification recommendations for toxicities in paediatric patients with chronic hepatitis B or chronic hepatitis C

Toxicity	Pegasys Dose Modification
Neutropenia	500 to <750 cells/mm^3: Immediate 1 level adjustment. 250 to <500 cells/mm^3: interrupt dosing until ≥1 000 cells/mm^3, then resume dose with 2 level adjustments and monitor. <250 cells/mm^3 (or febrile neutropenia): discontinue treatment.
Thrombocytopenia	Platelet 25 000 to <50 000 cells/mm^3: 2 level adjustment. Platelet <25 000 cells/mm^3: discontinue treatment.
Increased alanine aminotransferase (ALT)	For persistent or increasing elevations ≥5 but <10 x ULN, reduce dose with a 1 level adjustment and monitor weekly ALT level to ensure it is stable or decreasing. For persistent ALT values ≥10 x ULN discontinue treatment.

Dose adjustment in paediatric patients – dual therapy with Pegasys and ribavirin

For children and adolescents aged 5 to 17 years with CHC, the recommended dose of ribavirin is based on the patient's body weight, with a target dose of 15 mg/kg/day, divided in two daily doses. For children and adolescents 23 kg or greater, a dosing schedule using 200 mg ribavirin tablets is provided in Table 7. Patients and caregivers must not attempt to break the 200 mg tablets.

Table 7: Ribavirin dosing recommendations for paediatric patients with chronic hepatitis C aged 5 to 17 years

Body weight kg (lbs)	Ribavirin daily dose (Approx. 15 mg/kg/day)	Ribavirin number of tablets
23 – 33 (51-73)	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
34 – 46 (75-101)	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
47 – 59 (103-131)	800 mg/day	2 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
60 – 74 (132-163)	1 000 mg/day	2 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.
≥75 (>165)	1 200 mg/day	3 x 200 mg tablets A.M. 3 x 200 mg tablets P.M.

It is important to note that ribavirin should never be given as monotherapy. Unless otherwise noted, the management of all other toxicities should follow the adult recommendations.

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

Table 8: Ribavirin dose modification recommendations in paediatric patients with chronic hepatitis C

Full dose (Approx. 15 mg/kg/day)	One step dose modification (Approx. 7.5 mg/kg/day)	Ribavirin number of tablets
400 mg/day	200 mg/day	1 x 200 mg tablets A.M.
600 mg/day	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
800 mg/day	400 mg/day	1 x 200 mg tablets A.M. 1 x 200 mg tablets P.M.
1 000 mg/day	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.
1 200 mg/day	600 mg/day	1 x 200 mg tablets A.M. 2 x 200 mg tablets P.M.

Special populations

Elderly

Adjustments in the recommended dosage PEG-IFN-α-2a are not necessary when instituting Pegasys therapy in elderly patients (see section 5.2).

Renal impairment

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

Hepatic impairment
In patients with compensated cirrhosis (e.g., Child-Pugh A), Pegasys has been shown to be effective and safe. No PEG-IFN-α-2a dose adjustment is required for adult patients with mild liver impairment. Pegasys has not been evaluated in patients with decompensated cirrhosis (e.g., Child-Pugh B or C or bleeding oesophageal varices) and is contraindicated in these patients (see section 4.3). The Child-Pugh classification divides patients into groups A, B, and C, or "Mild", "Moderate" and "Severe" corresponding to scores of 5-6, 7-9 and 10-15, respectively.

Modified Assessment

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

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

Paediatric population (myeloproliferative neoplasms)
Pegasys is contraindicated in neonates and young children up to 3 years old due to the excipient benzyl alcohol (see sections 4.3 and 4.4).
The safety and efficacy of Pegasys in children and adolescents with myeloproliferative neoplasms has not been established. No data are available.
There is limited experience with Pegasys in treating paediatric patients with CHC aged 3 to 5 years, or who have failed to be adequately treated previously. There are no data in paediatric patients coinfected with HCV/HIV or with renal impairment.

Method of administration
Pegasys is administered subcutaneously in the abdomen or thigh. Exposure to Pegasys was decreased in studies following administration of Pegasys in the arm (see section 5.2).
Pegasys is designed for administration by the patient or carer. Each syringe should be used by one person only and is for single use.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Pegasys therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alfa interferons. All patients should be closely monitored for any signs or symptoms of psychiatric disorders. If symptoms of psychiatric disorders appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with Pegasys be discontinued, and the patient followed, with psychiatric intervention as appropriate.
Patients with existence of, or history of severe psychiatric conditions: If treatment with Pegasys is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition. The use of Pegasys in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3).
Patients with substance use/abuse: HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alfa interferon. If treatment with alfa interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Growth and development (children and adolescents):
During therapy with Pegasys +/- ribavirin lasting up to 48 weeks in patients aged 3 to 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1).
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials on a case by case basis (see sections 4.8 and 5.1). It is important to consider the treatment with Pegasys +/- ribavirin induced a growth inhibition during treatment, the reversibility of which is uncertain.
The risk of growth inhibition should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (for HBV-infection mainly HBV genotype and ALT levels; for HCV-infection mainly HCV genotype and HCV-RNA levels) (see section 5.1).
Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long-term effects on sexual maturation

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 cells/mm^3
- ANC ≥ 1 500 cells/mm^3
- Adequately controlled thyroid function (TSH and T4)

Haematological tests should be repeated after 2 and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy (including glucose monitoring).
In clinical trials, Pegasys treatment was associated with decreases in both total white blood cell (WBC) count and ANC, usually starting within the first 2 weeks of treatment (see section 4.8). Progressive decreases after 8 weeks of therapy were infrequent. The decrease in ANC was reversible upon dose reduction or cessation of therapy (see section 4.2), reached normal values by 8 weeks in the majority of patients and returned to baseline in all patients after about 16 weeks.
Pegasys treatment has been associated with decreases in platelet count, which returned to pre-treatment levels during the post-treatment observation period (see section 4.8). In some cases, dose modification may be necessary (see section 4.2).
The occurrence of anaemia (haemoglobin <10 g/dL) has been observed in up to 15% of CHC patients in clinical trials on the combined treatment of Pegasys with ribavirin. The frequency depends on the treatment duration and the dose of ribavirin (see section 4.8). The risk of developing anaemia is higher in the female population.

Caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.
Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a peginterferon and ribavirin concomitantly with azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon re-introduction of either treatment alone (see section 4.5).
The use of Pegasys and ribavirin combination therapy in CHC patients who failed prior treatment has not been adequately studied in patients who discontinued prior therapy for haematological adverse reactions. Physicians considering treatment in these patients should carefully weigh the risks versus the benefits of re-treatment.

Endocrine system
Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alfa interferons, including Pegasys. Prior to initiation of Pegasys therapy, TSH and T4 levels should be evaluated. Pegasys treatment may be initiated or continued if TSH levels can be maintained in the normal range by pharmaceutical means. TSH levels should be determined during the course of therapy if a patient develops clinical symptoms consistent with possible thyroid dysfunction (see section 4.8). Hypoglycaemia, hyperglycaemia and diabetes mellitus have been observed with Pegasys (see section 4.8). Patients with these conditions who cannot be effectively controlled by medication should not begin Pegasys monotherapy or Pegasys/ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Pegasys or Pegasys/ribavirin therapy (see section 4.3).

Cardiovascular system
Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alfa interferon therapies, including Pegasys. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of Pegasys therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. In patients with cardiovascular disease, anaemia may necessitate dose reduction or discontinuation of ribavirin (see section 4.2).

Liver function
In patients who develop evidence of hepatic decompensation during treatment, Pegasys should be discontinued. Increases in ALT levels above baseline have been observed in patients treated with Pegasys, including CHC and CHB patients with a viral response. Liver enzymes and hepatic function should be regularly controlled in patients with long-term Pegasys therapy. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued (see sections 4.2 and 4.8).
In CHB, unlike CHC, disease exacerbations during therapy are not uncommon and are characterised by transient and potentially significant increases in

serum ALT. In clinical trials with Pegasys in HBV, marked transaminase flares have been accompanied by mild changes in other measures of hepatic function and without evidence of hepatic decompensation. In approximately half the cases of flares exceeding 10x ULN, Pegasys dosing was reduced or withheld until the transaminase elevations subsided, while in the rest therapy was continued unchanged. More frequent monitoring of hepatic function was recommended in all instances.

Hypersensitivity

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

Autoimmune disease

The development of auto-antibodies and autoimmune disorders has been reported during treatment with alfa interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be re-assessed (see also *Endocrine system* in sections 4.4 and 4.8).

Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with CHC treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Fever/infections

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

Ocular changes

Retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction which may result in loss of vision have been reported in rare instances with Pegasys. All patients should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination. Adult and paediatric patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during Pegasys therapy. Pegasys treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Pulmonary changes

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

Skin disorder

Use of alfa interferons has been associated with exacerbation or provocation of psoriasis and sarcoidosis. Pegasys must be used with caution in patients with psoriasis, and in cases of onset or worsening of psoriatic lesions, discontinuation of therapy should be considered.

Transplantation

The safety and efficacy of Pegasys and ribavirin treatment have not been established in patients with liver and other transplantations. Liver and renal graft rejections have been reported with Pegasys, alone or in combination with ribavirin.

HIV-HCV co-infection

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

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

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

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

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

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

Dental and periodontal disorders

Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Pegasys and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Pegasys and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Excipients

This medicinal product contains benzyl alcohol. Benzyl alcohol may cause allergic reactions. Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome").Must not be given to premature babies or neonates. May cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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

HCV monoinfected patients and HBV monoinfected patients

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

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading

to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of peginterferon alfa-2a and ribavirin concomitantly with azathioprin should be avoided. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicinal products should be stopped (see section 4.4).
Results from pharmacokinetic sub studies of pivotal phase III trials demonstrated no pharmacokinetic interaction of lamivudine on Pegasys in HBV patients or between Pegasys and ribavirin in HCV patients.
A clinical trial investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration for the treatment of HBV, indicates that the combination is associated with an increased risk for developing peripheral neuropathy. The mechanism behind these events is not known; thus, co-treatment with telbivudine and other interferons (pegylated or standard) may also entail an excess risk. Moreover, the benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established.
Therefore, the combination of Pegasys with telbivudine is contraindicated (see section 4.3).
<u>HIV-HCV co-infected patients</u>
No apparent evidence of drug interaction was observed in 47 HIV-HCV co-infected patients who completed a 12-week pharmacokinetic sub study to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine and zidovudine or stavudine). However, due to high variability, the confidence intervals were quite wide. Plasma exposure of ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).
Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased *in vitro* when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactataemia/lactic acidosis have been reported with use of ribavirin.
Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral therapy regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

4.6 Fertility, Pregnancy and lactation

Pregnancy

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

Breastfeeding

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

Fertility

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

Use with ribavirin

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Polycythaemia vera and essential thrombocythaemia

Results from clinical studies and retrospective analyses in patients with polycythaemia vera and essential thrombocythaemia did not show any additional side effects than what is observed in patients with CHB or CHC, and as listed in Table 9.

The most frequent side effects are flu-like symptoms, injection site reactions, peripheral sensory neuropathies, visual disturbances, Grade 1/2 depression, leukopenia, increases in hepatic ASAT transaminases, hypertension, fatigue,

lymphopenia, anaemia and lymphocytopenia, diarrhoea, nausea, headache, musculoskeletal pain, skin toxicity, asthenia, and gastrointestinal symptoms.

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

Chronic hepatitis C in adult patients
The frequency and severity of the most commonly reported adverse reactions with Pegasys are similar to those reported with interferon alfa-2a (see Table 9). The most frequently reported adverse reactions with Pegasys 180 micrograms were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy.
Chronic hepatitis C in prior non-responder patients
Overall, the safety profile for Pegasys in combination with ribavirin in prior non-responder patients was similar to that in naïve patients. In a clinical trial of non-responder patients to prior pegylated interferon alfa-2b/ribavirin, which exposed patients to either 48 or 72 weeks of treatment, the frequency of withdrawal for adverse events or laboratory abnormalities from Pegasys treatment and ribavirin treatment was 6% and 7%, respectively, in the 48 week arms and 12% and 13%, respectively, in the 72 week arms. Similarly for patients with cirrhosis or transition to cirrhosis, the frequencies of withdrawal from Pegasys treatment and ribavirin treatment were higher in the 72-week treatment arms (13% and 15%) than in the 48-week arms (6% and 6%). Patients who withdrew from previous therapy with pegylated interferon alfa-2b/ribavirin because of haematological toxicity were excluded from enrolling in this trial.
In another clinical trial, non-responder patients with advanced fibrosis or cirrhosis (Ishak score of 3 to 6) and baseline platelet counts as low as 50,000 cells/mm^3 were treated for 48 weeks. Haematologic laboratory abnormalities observed during the first 20 weeks of the trial included anaemia (26% of patients experienced a haemoglobin level of <10 g/dL), neutropenia (30% experienced an ANC <750 cells/mm^3), and thrombocytopenia (13% experienced a platelet count <50 000 cells/mm^3) (see section 4.4).

Chronic hepatitis C and HIV co-infection
In HIV-HCV co-infected patients, the clinical adverse reaction profiles reported for Pegasys, alone or in combination with ribavirin, were similar to

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

Tabulated list of adverse reactions

Table 9 summarises the undesirable effects reported with Pegasys monotherapy in CHB or CHC adult patients and with Pegasys in combination with ribavirin in CHC patients. Undesirable effects reported in clinical studies are grouped according to frequency as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1°000 to < 1/100), rare (≥ 1/10°000 to < 1/1°000), very rare (< 1/10°000). For spontaneous reports of undesirable effects from post-marketing experience, the frequency is not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

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

Body system	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Infections and infestations		Bronchitis, upper respiratory infection, oral candidiasis, herpes simplex, fungal, viral and bacterial infections	Pneumonia, skin infection	Endocarditis, otitis externa		Sepsis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Hepatic neoplasm			
Blood and lymphatic system disorders		Thrombocytopenia, anaemia, lymphadenopathy		Pancytopenia	Aplastic anaemia	Pure red cell aplasia

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Immune system disorders			Sarcoidosis, thyroiditis	Anaphy-laxis, systemic lupus erythema-tosus rheumatoid arthritis	Idiopathic or thrombotic thrombocyto penic purpura	Liver and renal graft rejection, Vogt-Koyanagi-Harada disease
Endocrine disorders		Hypothyroid ism, hyperthyroid ism	Diabetes	Diabetic ketoacidosis		
Metabolism and nutrition disorders	Anorexia		Dehydration			
Psychiatric disorders	Depression* , anxiety, insomnia*	Aggression, mood alteration, emotional disorders, nervousness, libido decreased	Suicidal ideation, hallucina-tions	Suicide, psychotic disorder		Mania, bipolar disorders, homicidal ideation
Nervous system disorders	Headache, dizziness*, concentratio n impaired	Syncope, migraine, memory impairment, weakness, hypoaesthesi a, hyperaesthes ia, paraesthesia, tremor, taste disturbance, nightmares, somnolence	Peripheral neuropathy	Coma, convulsions, facial palsy		Cerebral ischaemia
Eye disorders		Vision blurred, eye pain, eye inflammatio n, xerophthalm ia	Retinal haemorrhage	Optic neuropathy, papilloedem a, retinal vascular disorder, retinopathy, corneal ulcer	Vision loss	Serous retinal detachment, Optic neuritis
Ear and labyrinth disorders		Vertigo, earache	Hearing loss			

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Cardiac disorders		Tachycardia, oedema peripheral, palpitations		Myocardial infarction, congestive heart failure, cardiomyopathy, angina, arrhythmia, atrial fibrillation, pericarditis, supraventricular tachycardia		
Vascular disorders		Flushing	Hypertension	Cerebral haemorrhage, vasculitis		Peripheral ischaemia
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough	Dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, nasal congestion, rhinitis, sore throat	Wheezing	Interstitial pneumonitis including fatal outcome, pulmonary embolism		Pulmonary arterial hypertension [§]
Gastrointestinal disorders	Diarrhoea*, nausea*, abdominal pain*	Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, dry mouth	Gastrointestinal bleeding	Peptic ulcer, pancreatitis		Ischaemic colitis, tongue pigmentation
Hepatobiliary disorders			Hepatic dysfunction	Hepatic failure, cholangitis, fatty liver		
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, pruritis, dry skin	Psoriasis, urticaria, eczema, rash, sweating increased, skin disorder, photosensitivity reaction, night sweats			Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, erythema multiforme	

Body system	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps		Myositis		Rhabdomyolysis
Renal and urinary disorders				Renal insufficiency		
Reproductive system and breast disorders		Impotence				
General disorders and administration site conditions	Pyrexia, rigours*, pain*, asthenia, fatigue, injection site reaction*, irritability*	Chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst				
Investigations		Weight decreased				
Injury, poisoning and procedural complications				Substance overdose		

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

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

Description of selected adverse reactions

Pulmonary arterial hypertension

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

Laboratory values

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

Treatment with Pegasys was associated with decreases in haematological values (leucopenia, neutropenia, lymphopenia, thrombocytopenia and haemoglobin), which generally improved with dose modification, and returned to pre-treatment levels within 4-8 weeks upon cessation of therapy (see sections 4.2 and 4.4).

Moderate (ANC: 0.749 - 0.5 x 10^9/L) and severe (ANC: < 0.5 x 10^9/L) neutropenia was observed respectively in 24% (216/887) and 5% (41/887) of patients receiving Pegasys 180 micrograms and ribavirin 1 000/1 200 milligrams for 48 weeks.

Anti-interferon antibodies

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

Thyroid function

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

Laboratory values for HIV-HCV co-infected patients

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

Paediatric population

Chronic hepatitis B

In a clinical trial (YV25718) with 111 paediatric patients (3 to 17 years of age) treated with Pegasys for 48 weeks, the safety profile was consistent with that seen in adults with CHB and in paediatric patients with CHC.

The mean changes from baseline in height and weight for age Z-scores at Week 48 of treatment in study YV25718 were -0.07 and -0.21(n=108 and n= 106 respectively) for Pegasys-treated patients as compared to - 0.01 and -0.08 (n=47 each) in untreated patients. At Week 48 of Pegasys treatment, a height or weight percentile decrease of more than 15 percentiles on the normative growth curves was observed in 6% of patients for height and 13% of patient for weight, whereas in the untreated group it was 2% of patients for height and 9% for weight. Post-treatment recovery in growth was observed in the majority of patients in short-term (81%up to 2 years) and long-term follow-up (82%up to 5 years) studies.

Chronic hepatitis C

In a clinical trial with 114 paediatric patients (5 to 17 years of age) treated with Pegasys alone or in combination with ribavirin (see section 5.1), dose modifications were required in approximately one-third of patients, most commonly for neutropenia and anaemia. In general, the safety profile observed in paediatric patients was similar to that seen in adults. In the paediatric study, the most prevalent adverse reactions in patients treated with combination therapy for up to 48 weeks with Pegasys and ribavirin were influenza-like illness (91%), headache (64%), gastrointestinal disorder (56%), and injection-site reaction (45%). A full listing of adverse reactions reported in this treatment group (n=55) is provided in Table 10. Seven patients receiving combination Pegasys and ribavirin treatment for 48 weeks discontinued therapy for safety reasons (depression, psychiatric evaluation abnormal, transient blindness, retinal exudates, hyperglycaemia, type 1 diabetes mellitus, and anaemia). Most of the adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 2 patients in the Pegasys plus ribavirin combination therapy group (hyperglycaemia and cholecystectomy).

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

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

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

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

Laboratory values

Decreases in haemoglobin, neutrophils, platelets or increased ALT may require dose reduction or permanent discontinuation from treatment (see section 4.2). Most laboratory abnormalities noted during the clinical trial returned to baseline levels shortly after discontinuation of treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse (see details below)

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Overdoses involving between two injections on consecutive days (instead of weekly interval) up to daily injections for 1 week (i.e., 1 260 micrograms/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 and 630 micrograms have been administered in renal cell carcinoma and chronic myelogenous leukaemia clinical trials, respectively. Dose limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia, consistent with interferon therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB11

Mechanism of action

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

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

Pharmacodynamic effects

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received treatment with 180 micrograms Pegasys. The first phase of decline occurs 24 to 36 hours after the first dose of Pegasys and is followed by the second phase of decline which continues over the next 4 to

16 weeks in patients who achieve a sustained response. Ribavirin had no significant effect on the initial viral kinetics over the first 4 to 6 weeks in patients treated with the combination of ribavirin and pegylated interferon alfa-2a or interferon alfa.

Clinical efficacy and safety
Polycythaemia vera and essential thrombocythemia

The efficacy results are primarily based on bibliographical data from two prospective, investigator-initiated, open-label studies, MPD-RC 112 and MPD-RC 111.

Study MPD-RC 112
The randomised, investigator-initiated, open-label, multicenter, phase III trial conducted by the Myeloproliferative Disorders Research Consortium (MPD-RC) compared hydroxyurea (HU) to PEG-IFN-α-2a in treatment-naïve (TN), high-risk patients with essential thrombocythaemia (ET; n=81) or polycythaemia vera (PV; n=87) (NCT01259856/MPD-RC 112). The primary endpoint was complete response (CR) rate according to European LeukaemiaNet (ELN) criteria at 12 months of treatment. CR was defined as a platelet count $<400x10^9$/L, HCT <45% without phlebotomy for patients with PV only, white blood cell count $<10x10^9$/L, resolution of splenomegaly, and resolution of disease-related symptoms (microvascular disturbances, headache, and pruritus). PEG-IFN-α-2a was self-administered s.c. at 45 micrograms/week and titrated in 45 micrograms increments monthly to a maximum of 180 micrograms/week. HU was initiated at 500 mg twice daily. A total of 168 patients were enrolled and randomised to treatment arms (86 HU, 82 PEG-IFN-α-2a). At baseline, mean age was 63 and 60 years and mean duration of ET/PV was 3.1 and 2.6 months in the HU and PEG-IFN-α-2a arms, respectively. The median duration of treatment was 81.0 weeks and 94.6 weeks in the HU and PEG-IFN-α-2a arms, respectively. Seventy-four percent of patients receiving HU and 87% of patients receiving PEG-IFN-α-2a were treated for 12 months or longer. Table 11 displays the response by treatment arm.

Table 11: Response by treatment arm after 12 months in study MPD-RC 112

	HU (n=86), %	PEG (n=82), %
Complete response (CR) ET PV	32 (37%) 19 (45%) 13 (30%)	29 (35%) 17 (44)% 12 (28%)

Study MPD-RC 111
This single-arm, open-label, multicenter phase II trial also conducted by the MPD-RC, evaluated the hematologic response to PEG-IFN-α-2a in 50 PV and 65 ET patients who were resistant or intolerant to HU (NCT01259817/MPD-RC 111). The primary endpoint was CR or PR rate at 12 months of treatment according to ELN criteria. PEG-IFN α 2a was self-administered s.c. at 45 micrograms/week and titrated in 45 micrograms increments monthly to a maximum of 180 micrograms/week. Median duration of treatment was 78.5 and 82 months in ET and PV patients, respectively.
In ET patients, CR and PR at 12 months were observed in 28 (43.1%) and 17 (26.2%) patients, for an overall response rate (ORR) of 69.2% (95% CI, 56.6%-80.0%). In PV patients, 11 (22%) attained a CR and 19 (38%) a PR, for an ORR of 60% (95% CI, 45.2%-73.6%).
Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Pegasys in all subsets of the paediatric population in the treatment of polycythaemia vera and essential thrombocythaemia (see section 4.2 for information on paediatric use).

Chronic hepatitis B
Predictability of response
A patient-level meta-analysis of 9 Pegasys clinical studies (n=1,423) in CHB HBeAg positive and HBeAg-negative patients demonstrated that HBsAg and HBV DNA levels at Week 12 of treatment, are predictive of final treatment outcome at Week 24 post-treatment in certain genotypes. Operating characteristics of these biomarkers are presented in Table 12. No single biomarker with a cut-off can be identified to optimize all the operating characteristics (negative predictive value [NPV], sensitivity, specificity) and practical characteristics (simplicity, convenience). Consideration for early treatment discontinuation should be evaluated in the context of a particular clinical situation.
For HBeAg-positive patients with HBV genotype B and C infection, HBsAg > 20 000 IU/mL or HBV DNA > 8 $\log_{10}$ IU/mL at Week 12 following commencement of treatment is associated with high likelihood of failure to achieve HBeAg seroconversion and HBV-DNA <2 000 IU/mL at 24 week post-treatment (NPV > 90%). For HBV genotype A and D, subgroup size was insufficient to be analysed.
For HBeAg-negative patients with HBV genotype D infection, HBsAg > 20 000 IU/mL or HBV DNA > 6.5 $\log_{10}$ IU/mL at Week 12 following commencement of treatment is associated with high likelihood of failure to achieve HBV-DNA <2 000 IU/mL and ALT normalization at Week 24 post treatment. HBV genotype A subgroup size was insufficient to be analysed. No biomarker can be identified with acceptable performance for HBeAg-negative patients with HBV genotype B or C infection.
Other published on-treatment biomarkers that are predictive of the final outcome of Pegasys treatment may be considered.

Table 12: Performance of individual biomarkers at Week 12 of therapy in CHB HBeAg-positive and HBeAg-negative patients according to genotype

Genotype	Cut-off (IU/mL)	NPV	Sensitivity	Specificity

HBeAg-positive[(a)]				
B	HBsAg > 20°000	0.93	0.96	0.23
	HBV DNA > 8 $\log_{10}$	0.90	0.94	0.26
C	HBsAg > 20°000	0.96	0.97	0.22
	HBV DNA > 8 $\log_{10}$	0.98	0.98	0.19
HBeAg-negative[(a)]				
D	HBsAg > 20°000	0.91	0.94	0.16
	HBV DNA > 6.5 $\log_{10}$	1.00	1.00	0.11

NPV= negative predictive value; Sensitivity = % of all responders not meeting the stopping rule; Specificity = % of all non-responders meeting stopping rule

(a) Treatment response for HBeAg-positive patients was defined as HBeAg seroconversion (defined as loss of HBeAg and presence of anti-HBe) + HBV DNA <2 000 IU/mL at 6 months post-treatment and treatment response for HBeAg-negative patients was defined as HBV DNA < 2 000 IU/mL + ALT normalization at 6 months post-treatment.

All clinical trials recruited patients with CHB who had active viral replication measured by HBV DNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. Study WV16240 recruited patients who were positive for HBeAg, while study WV16241 recruited patients who were negative for HBeAg and positive for anti-HBe. In both studies the treatment duration was 48 weeks, with 24 weeks of treatment-free follow-up. Both studies compared Pegasys plus placebo vs Pegasys plus lamivudine vs lamivudine alone. No HBV-HIV co-infected patients were included in these clinical trials.
Response rates at the end of follow-up for the two studies are presented in Table 13. In study WV16240, the primary efficacy endpoints were HBeAg seroconversion and HBV-DNA below 10^5 copies/mL. In study WV16241, the primary efficacy endpoints were ALT normalisation and HBV-DNA below 2 x 10^4 copies/mL. HBV-DNA was measured by the COBAS AMPLICOR™ HBV MONITOR Assay (limit of detection 200 copies/mL).
A total of 283/1°351 (21%) of patients had advanced fibrosis or cirrhosis, 85/1 351 (6%) had cirrhosis. There was no difference in response rate between these patients and those without advanced fibrosis or cirrhosis.

Table 13: Serological, virological and biochemical responses in chronic hepatitis B

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

*For HBeAg-positive patients: HBV DNA $< 10^5$ copies/mL
For HBeAg-negative/anti-HBe-positive patients: HBV DNA $< 2 \times 10^4$ copies/mL
#p-value (vs. lamivudine) $\leq$ 0.01 (stratified Cochran-Mantel-Haenszel test)

Histological response was similar across the three treatment groups in each study; however, patients showing a sustained response 24 weeks after the end of treatment were significantly more likely to also show histological improvement.
All patients who completed the phase III studies were eligible for entry into a long-term follow-up study (WV16866). Among patients from study WV16240, who received Pegasys monotherapy and entered the long-term follow-up study, the rate of sustained HBeAg seroconversion 12 months after the end of therapy was 48% (73/153). In patients receiving Pegasys monotherapy in study WV16241, the rate of HBV DNA response and ALT normalisation 12 months after end of treatment were 42% (41/97) and 59% (58/99), respectively.

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

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

Confirmatory clinical trials in adult treatment-naïve patients
All clinical trials recruited interferon-naïve patients with CHC 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 22). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µL.
For HCV monoinfected patients and HIV-HCV co-infected patients, for treatment regimens, duration of therapy and study outcome see Tables 14, 15, 16 and Table 22, 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 14: Virological response in CHC patients

	Pegasys monotherapy				**Pegasys combination therapy**		
	non-cirrhotic and cirrhotic		**cirrhotic**		**non-cirrhotic and cirrhotic**		
	Study NV15496 + NV15497 + NV15801		**Study NV15495**		**Study NV15942**	**Study NV15801**	
	Pegasys 180 mcg (N=701) 48 weeks	**Interferon alfa-2a** 6 MIU/3 MIU & 3 MIU (N=478) 48 weeks	**Pegasys** 180 mcg (N=87) 48 weeks	**Interferon alfa-2a** 3 MIU (N=88) 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1°000/1°200 mg (N=436) 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1°000/1°200 mg (N=453) 48 weeks	**Interferon alfa-2b** 3 MIU & **Ribaviri n** 1°000/1° 200 mg (N=444) 48 weeks
Response at End of Treatment	55 - 69%	22 - 28%	44%	14%	68%	69%	52%
Overall Sustained Response	28 - 39%	11 - 19%	30%*	8%*	63%	54%**	45%**

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

The virological responses of HCV monoinfected patients treated with Pegasys and ribavirin combination therapy in relation to genotype and pre-treatment viral load and in relation to genotype, pre-treatment viral load and rapid virological response at week 4 are summarised in Table 15 and Table 16, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype, baseline viral load and virological response at week 4 (see Tables 1, 15 and 16).
The difference between treatment regimens was in general not influenced by presence/absence of cirrhosis; therefore, treatment recommendations for genotype 1, 2 or 3 are independent of this baseline characteristic.

Table 15: Sustained virological response based on genotype and pre-treatment viral load after Pegasys combination therapy with ribavirin in CHC patients

	Study NV15942				Study NV15801	
	Pegasys 180 mcg & **Ribavirin** 800 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1 000/1 200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1 000/1 200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1 000/1 200 mg 48 weeks	**Interferon alfa-2b** 3 MIU & **Ribavirin** 1 000/1 200 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)

Low viral load = ≤ 800 000 IU/mL; High viral load = > 800 000 IU/mL
*Pegasys 180 mcg & ribavirin 1 000/1 200 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 1 000/1 200 mg, 48 w *vs.* Pegasys 180 mcg & ribavirin 1 000/1 200 mg, 24 w: Odds Ratio (95% CI) = 2.12 (1.30 to 3.46), P-value (stratified Cochran-Mantel-Haenszel test) = 0.002.

The possibility to consider shortening treatment duration to 24 weeks in genotype 1 and 4 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response at week 4 in studies NV15942 and ML17131 (see Table 16).

Table 16: Sustained virological response based on rapid viral response at week 4 for genotype 1 and 4 after Pegasys combination therapy with ribavirin in CHC patients

	Study NV15942		Study ML17131
	Pegasys 180 mcg & **Ribavirin** 1 000/1 200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1 000/1 200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1 000/1 200 mg 24 weeks
Genotype 1 RVR	90% (28/31)	92% (47/51)	77% (59/77)
Low viral load	93% (25/27)	96% (26/27)	80% (52/65)
High viral load	75% (3/4)	88% (21/24)	58% (7/12)
Genotype 1 non RVR	24% (21/87)	43% (95/220)	-
Low viral load	27% (12/44)	50% (31/62)	-
High viral load	21% (9/43)	41% (64/158)	
Genotype 4 RVR	(5/6)	(5/5)	92% (22/24)
Genotype 4 non RVR	(3/6)	(4/6)	-

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

Although limited, data indicated that shortening treatment to 24 weeks might be associated with a higher risk of relapse (see Table 17).

Table 17: Relapse of virological response at the end of treatment for rapid virological response population

	Study NV15942		Study NV15801
	Pegasys 180 mcg & **Ribavirin** 1 000/1 200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1 000/1 200 mg 48 weeks	**Pegasys** 180 mcg & **Ribavirin** 1 000/1 200 mg 48 weeks
Genotype 1 RVR	6.7% (2/30)	4.3% (2/47)	0% (0/24)
Low viral load	3.8% (1/26)	0% (0/25)	0% (0/17)
High viral load	25% (1/4)	9.1% (2/22)	0% (0/7)
Genotype 4 RVR	(0/5)	(0/5)	0% (0/4)

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on a sustained virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 18).
In study NV17317 in patients infected with viral genotype 2 or 3, all patients received Pegasys 180 mcg sc qw and a ribavirin dose of 800 mg and were randomised to treatment for either 16 or 24 weeks. Overall treatment for 16 weeks resulted in lower sustained viral response (65%) than treatment for 24 weeks (76%) ($p < 0.0001$).
The sustained viral response achieved with 16 weeks of treatment and with 24 weeks of treatment was also examined in a retrospective subgroup analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline (see Table 18).

Table 18: Sustained virological response overall and based on rapid viral response by week 4 for genotype 2 or 3 after Pegasys combination therapy with ribavirin in CHC patients

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

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

It is presently not clear whether a higher dose of ribavirin (e.g. 1 000/1 200 mg/day based on body weight) results in higher SVR rates than does the 800 mg/day, when treatment is shortened to 16 weeks.
The data indicated that shortening treatment to 16 weeks is associated with a higher risk of relapse (see Table 19).

Table 19: Relapse of virological response after the end of treatment in genotype 2 or 3 patients with a rapid viral response

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

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

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

Adult chronic hepatitis C prior treatment non-responder patients

In study MV17150, patients who were non-responders to previous therapy with pegylated interferon alfa-2b plus ribavirin were randomised to four different treatments:

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

All patients received ribavirin (1 000 or 1 200 mg/day) in combination with Pegasys. All treatment arms had 24 week treatment-free follow-up. Multiple regression and pooled group analyses evaluating the influence of treatment duration and use of induction dosing clearly identified treatment duration for 72 weeks as the primary driver for achieving a sustained virological response. Differences in sustained virological response (SVR) based on treatment duration, demographics and best responses to previous treatment are displayed in Table 20.

Table 20: Week 12 virological response (VR) and sustained virological response (SVR) in patients with virological response at week 12 after treatment with Pegasys and ribavirin combination therapy in non-responders to peginterferon alfa-2b plus ribavirin

Study MV17150			
	Pegasys 360/180 or 180 mcg & **Ribavirin** 1 000/1 200 mg 72 or 48 weeks (N = 942) **Pts with VR at Wk 12 [a] (N = 876)**	**Pegasys** 360/180 or 180 mcg & **Ribavirin** 1 000/1 200 mg 72 weeks (N = 473) **SVR in Pts with VR at Wk 12 [b] (N = 100)**	**Pegasys** 360/180 or 180 mcg & **Ribavirin** 1 000/1 200 mg 48 weeks (N = 469) **SVR in Pts with VR at Wk 12 [b] (N = 57)**
Overall	18% (157/876)	57% (57/100)	35% (20/57)
Low viral load	35% (56/159)	63% (22/35)	38% (8/21)
High viral load	14% (97/686)	54% (34/63)	32% (11/34)
Genotype 1/4	17% (140/846)	55% (52/94)	35% (16/46)
Low viral load	35% (54/154)	63% (22/35)	37% (7/19)
High viral load	13% (84/663)	52% (30/58)	35% (9/26)
Genotype 2/3	58% (15/26)	(4/5)	(3/10)
Low viral load	(2/5)	—	(1/2)
High viral load	(11/19)	(3/4)	(1/7)
Cirrhosis Status			
Cirrhosis	8% (19/239)	(6/13)	(3/6)
Non-cirrhosis	22% (137/633)	59% (51/87)	34% (17/50)
Best Response during Previous Treatment			
≥2log$_{10}$ decline in HCV RNA	28% (34/121)	68% (15/22)	(6/12)
<2log$_{10}$ decline in HCV RNA	12% (39/323)	64% (16/25)	(5/14)
Missing best previous response	19% (84/432)	49% (26/53)	29% (9/31)

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

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

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

In the HALT-C study, patients with CHC and advanced fibrosis or cirrhosis who were non-responders to previous treatment with interferon alfa or pegylated interferon alfa monotherapy or in combination therapy with ribavirin were treated with Pegasys 180 mcg/week and ribavirin 1°000/1°200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on Pegasys plus ribavirin combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. The probability for sustained virological response varied depending upon the previous treatment regimen; see Table 21.

Table 21: Sustained virological response in HALT-C by previous treatment regimen in non-responder population

Previous Treatment	**Pegasys** 180 mcg & **Ribavirin** 1 000/1 200 mg 48 weeks
Interferon	27% (70/255)
Pegylated interferon	34% (13/38)
Interferon plus ribavirin	13% (90/692)
Pegylated interferon plus ribavirin	11% (7/61)

HIV-HCV co-infected patients

The virological responses of patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and pre-treatment viral load for HIV-HCV co-infected patients are summarised below in Table 22.

Table 22: Sustained virological response based on genotype and pre-treatment viral load after Pegasys combination therapy with ribavirin in HIV-HCV co-infected patients

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

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

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared treatment using Pegasys 180 mcg/week and either ribavirin

800 mg or 1 000 mg (<75 kg)/1 200 mg (≥75 kg) daily for 48 weeks. The study was not powered for efficacy considerations. The safety profiles in both ribavirin groups were consistent with the known safety profile of Pegasys plus ribavirin combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose ribavirin arm.

HCV patients with normal ALT

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

Paediatric population

Chronic hepatitis B

Study YV25718 was conducted in previously untreated paediatric patients aged 3 to 17 years (51% < 12 years old) with HBeAg positive CHB and ALT > ULN but < 10 x ULN in two blood samples taken ≥ 14 days apart during the 6 months before the first dose of study drug. Patients with cirrhosis were not enrolled in this study. A total of 151 patients without advanced fibrosis were 2:1 randomized to Pegasys (group A, n=101) or untreated control (group B, n=50), respectively. Patients with advanced fibrosis were assigned to Pegasys treatment (group C, n=10). Patients in groups A and C (n=111) were treated with Pegasys once weekly for 48 weeks according to BSA categories, whereas patients in group B were observed for a period of 48 weeks (principal observation period). Patients in group B had the choice to switch to treatment with Pegasys after Week 48 of the principal observation period. All patients were followed up for 24 weeks post-treatment (groups A and C), or post-principal observation period (group B). After the Week 24 follow-up visit, patients from group A, B and C entered a long-term follow-up period (lasting for 5 years after end of treatment). Response rates in groups A and B at the end of 24 weeks follow-up are presented in Table 23. Efficacy response in group C to Pegasys treatment was in line with that seen in group A. For paediatric patients, efficacy has not been established in HBV genotypes other than genotypes A-D.

Table 23: Serological, virological and biochemical responses in paediatric patients with chronic hepatitis B

	Group A (Pegasys treatment) (N=101)	**Group B** Untreated** (N=50)	**Odds Ratio** (95% CI)	**p-value**
HBeAg Seroconversion	25.7%	6.0%	5.4 (1.5 – 19.2)	0.0043 [1]
HBV DNA < 20,000 IU/mL*	33.7%	4.0%	12.2 (2.9 – 108.3)	<0.0001 [2]
HBV DNA < 2,000 IU/mL	28.7%	2.0%	19.7 (3.0 – 822.2)	<0.0001 [2]
ALT Normalization	51.5%	12.0%	7.8 (2.9 – 24.1)	<0.0001 [2]
HBsAg Seroconversion	7.9%	0.0%	-	0.0528 [2]
Loss of HBsAg	8.9%	0.0%	-	0.0300 [2]

* Similar to end point of HBV DNA < 10^5 copies/mL. COBAS AMPLICOR HBV MONITOR: HBV-DNA (IU/mL) = HBV-DNA (copies/mL) / 5.26)

** Patients switched to Pegasys treatment post-principal observation period and before Week 24 follow-up were counted as non-responders.

[1] Cochran-Mantel-Haenszel test, stratified by genotype (A vs. non-A) and baseline ALT (< 5 × ULN and >= 5 × ULN)

[2] Fisher's Exact Test

The response rate of HBeAg seroconversion was lower in patients with HBV genotype D, also in patients with no to minimal increase in ALT level at baseline (see Table 24).

Table 24: HBeAg seroconversion rates (%) by HBV genotype and baseline ALT levels

	Group A (Pegasys treatment) (N=101)	**Group B** Untreated** (N=50)	**Odds Ratio** (95% CI)
HBV genotype A	3/9 (33.3%)	1/3 (33.3%)	1.0 (0.04,78.4)
B	7/21 (33.3%)	0/6 (0.0%)	-
C	13/34 (38.2%)	1/23 (4.3%)	13.62 (1.7,604.5)
D*	3/31 (9.7%)	1/18 (5.6%)	1.8 (0.1,101.2)
Other	0/6 (0.0%)	0/0	-
ALT <1xULN	0/7 (0.0%)	0/5 (0.0%)	-
>=1xULN - <1.5xULN	2/22 (9.1%)	0/8 (0.0%)	-
>=1.5xULN - <2xULN	7/19 (36.8%)	0/11 (0.0%)	-
>=2xULN - <5xULN	15/43 (34.9%)	1/17 (5.9%)	8.6 (1.1,383.0)
>=5xULN - <10xULN	2/8 (25.0%)	2/9 (22.2%)	1.2 (0.06,20.7)
>=10xULN	0/2 (0.0%)	0/0	-

* Subgroup of patients with genotype D had a higher proportion with baseline ALT < 1.5x ULN (13/31) compared to other genotype groups (16/70).

** Patients switched to Pegasys treatment post-principal observation period and before Week 24 follow-up were counted as non-responders.

Exploratory analyses based on limited data show paediatric patients with greater decline in HBV-DNA at week 12 of therapy were more likely to achieve HBeAg seroconversion at 24 weeks of follow-up (Table 25).

Table 25: HBeAg seroconversion rates (%) by HBV-DNA decline from baseline to week 12 of Pegasys treatment in paediatric patients

	HBeAg seroconversion rates	By HBV-DNA (IU/mL) decline from baseline to week 12		
		<1 log_{10} decline	1 - <2 log_{10} decline	≥2 log_{10} decline
All genotypes (N=101)				
Responder	26/101 (25.7 %)	6/44 (13.6 %)	5/24 (20.8 %)	15/30 (50.0 %)
Genotype-A (N=9)				
Responder	3/9 (33.3 %)	0/6 (0.0 %)	2/2 (100.0 %)	1/1 (100.0 %)
Genotype-B (N=21)				
Responder	7/21 (33.3 %)	1/6 (16.7 %)	1/5 (20.0 %)	5/10 (50.0 %)
Genotype-C (N=34)				
Responder	13/34 (38.2 %)	3/10 (30.0 %)	2/12 (16.7 %)	8/12 (66.7 %)
Genotype-D (N=31)				
Responder	3/31 (9.7 %)	2/20 (10.0 %)	0/5 (0.0 %)	1/5 (20.0 %)

Chronic hepatitis C

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

In the NV17424 (PEDS-C) study, previously untreated paediatric patients 5 to 17 years of age (55% < 12 years old) with compensated CHC and detectable HCV RNA were treated with Pegasys 180 mcg x BSA/1.73 m^2 once weekly for 48 weeks with or without ribavirin 15 mg/kg/day. All patients were followed for 24 weeks post-treatment. A total of 55 patients received initial combination treatment of Pegasys plus ribavirin, of whom 51% were female, 82% were Caucasian, and 82% were infected with HCV genotype 1. The study efficacy results for these patients are summarised in Table 26.

Table 26: Sustained virological response in the NV17424 study

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

*Results indicate undetectable HCV-RNA defined as HCV RNA less than 50 IU/mL at 24 weeks post-treatment using the AMPLICOR HCV test v2.

**Scheduled treatment duration was 48 weeks regardless of the genotype

5.2 Pharmacokinetic properties

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

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

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

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

Linearity/non-linearity
Dose-proportional increases in exposure of Pegasys are seen in healthy subjects and in patients with chronic hepatitis B or C after once-weekly dosing.
In CHB or CHC patients, peginterferon alfa-2a serum concentrations accumulate 2 to 3 fold after 6 to 8 weeks of once weekly dosing compared to single dose values. There is no further accumulation after 8 weeks of once weekly dosing. The peak to trough ratio after 48 weeks of treatment is about 1.5 to 2. Peginterferon alfa-2a serum concentrations are sustained throughout one full week (168 hours).

Patients with renal impairment
A clinical trial evaluated 50 CHC patients with either moderate (creatinine clearance 30 to 50 mL/min) or severe (creatinine clearance less than 30 mL/min) renal impairment, or with end stage renal disease (ESRD) requiring chronic hemodialysis (HD). Patients with moderate renal impairment receiving Pegasys 180 mcg once weekly exhibited similar peginterferon alfa-2a plasma exposures compared to patients with normal renal function. Patients with severe renal impairment receiving Pegasys 180 mcg once weekly showed a 60% higher peginterferon alfa-2a exposure than patients with normal renal function, therefore a reduced dose of Pegasys 135 mcg once weekly is recommended in patients with severe renal impairment. In 13 patients with ESRD requiring chronic HD, administration of Pegasys 135 mcg once weekly resulted in 34% lower peginterferon alfa-2a exposure than in patients with normal renal function. However, several independent studies have demonstrated the 135mcg dose to be safe, efficacious and well tolerated, in patients with ESRD (see section 4.2).

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

Paediatric population
Pegasys pharmacokinetics have been characterized in paediatric patients with CHB (YV25718), as well as in paediatric patients with CHC (NR16141), using population pharmacokinetics. In both studies, Pegasys apparent clearance and apparent volume of distribution were related linearly to body size i.e. either BSA (NR16141) or body weight (YV25718).
From the YV25718 study, 31 paediatric patients 3 to 17 years of age with CHB participated in the PK sub-study and received Pegasys according to a BSA category dosing regimen. Based on the population pharmacokinetic model, the mean exposure (AUC) during the dosing interval for each BSA category was comparable with that observed in adults receiving 180 mcg fixed dosing.
From the NR16141study, 14 children 2 to 8 years of age with CHC received Pegasys monotherapy at a dose of: 180 mcg x BSA of the child/1.73 m^2. The PK model developed from this study shows a linear influence of BSA on the apparent clearance of the drug over the age range studied. Thus, the lower the BSA of the child, the lower the clearance of the drug and the higher the resultant exposure. The mean exposure (AUC) during the dosing interval is predicted to be 25% to 70% higher than that observed in adults receiving 180 mcg fixed dosing.
Pegasys pharmacokinetics have not been characterised in paediatric patients with polycythaemia vera and essential thrombocythaemia.

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 (1 663 vs. 1 295 ng·h/mL) but peak concentrations (9.1 vs. 10.3 ng/mL) were similar

in subjects older than 62 years. Based on drug exposure, pharmacodynamic response and tolerability, a lower dose of Pegasys is not needed in the geriatric patient (see section 4.2).

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

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

5.3 Preclinical safety data

The non-clinical toxicity studies conducted with Pegasys were limited due to species specificity of interferons. Acute and chronic toxicity studies have been carried out in cynomolgus monkeys, and the findings observed in peginterferon dosed animals were similar in nature to those produced by interferon alfa-2a.
Reproductive toxicity studies have not been performed with Pegasys. As with other alfa interferons, prolongation of the menstrual cycle was observed following administration of peginterferon alfa-2a to female monkeys. Treatment with interferon alfa-2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys. Although no teratogenic effects were seen in the offspring delivered at term, adverse effects in humans cannot be excluded.
Pegasys plus ribavirin
When used in combination with ribavirin, Pegasys did not cause any effects in monkeys not previously seen with either active substance alone. The major treatment-related change was reversible mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Polysorbate 80
Benzyl alcohol
Sodium acetate
Acetic acid
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special precautions for storage

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

6.5 Nature and contents of container

0.5 mL of solution for injection in pre-filled syringe (siliconised Type I glass) with a plunger stopper and tip cap (butyl rubber laminated on the product facing side with fluororesin) with a needle.
Pegasys 90 micrograms solution for injection in pre-filled syringe
The syringe is labelled with graduations corresponding to doses of 90 mcg, 65 mcg, 45 mcg, 30 mcg, 20 mcg and 10 mcg. Available in packs of 1 pre-filled syringe.
Pegasys 135 micrograms solution for injection in pre-filled syringe
The syringe is labelled with graduations corresponding to doses of 135 mcg, 90 mcg and 45 mcg. Available in packs of 1, 4 or a multipack of 12 (2 packs of 6) pre-filled syringes.
Not all pack sizes may be marketed.
Pegasys 180 micrograms solution for injection in pre-filled syringe

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

6.6 Special precautions for disposal

The solution for injection is for single use only. It should be inspected visually for particulate matter and discoloration before administration.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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