PFS-PEG-2021 12-0

Pegasys®

Peginterferon alfa-2a

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Immunostimulants/ Interferons
ATC code: L03A B11

1.2 Type of Dosage Form

Pegasys is supplied as a sterile, ready-to-use liquid for subcutaneous (SC) injection as prefilled syringes and vials:

- 180 mcg Pegasys prefilled syringe: each single use syringe contains 0.5 mL with 180 mcg peginterferon alfa-2a.
- 135 mcg Pegasys prefilled syringe: each single use syringe contains 0.5 mL with 135 mcg peginterferon alfa-2a.
- single dose vials: each vial contains 1.0 mL with 180 mcg of peginterferon alfa-2a.
- single dose vials: each vial contains 1.0 mL with 135 mcg of peginterferon alfa-2a.

1.3 Route of Administration

Subcutaneous injection

1.4 Sterile / Radioactive Statement

Not applicable

1.5 Qualitative and Quantitative Composition

Active ingredient: peginterferon alfa-2a.
Excipients:
As registered locally.

2 CLINICAL PARTICULARS

2.1 Therapeutic Indications

Pegasys is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC) in patients with compensated liver disease. This includes patients with compensated cirrhosis and patients with HIV disease that is clinically stable (e.g. antiretroviral therapy not required or receiving stable antiretroviral therapy).

The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. The combination of Pegasys and ribavirin is indicated in naive patients and patients who have failed previous treatment with interferon alpha (pegylated or non-pegylated) alone or in combination therapy with ribavirin.

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

Chronic Hepatitis B (CHB): Pegasys is indicated for the treatment of both HBeAg-positive and HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication and liver inflammation.

2.2 Dosage and Method of Administration

General

The safety and efficacy of alternating or switching between Pegasys and products that are biosimilar but not deemed interchangeable has not been established. Therefore, the benefit-risk of alternating or switching needs to be carefully considered.

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

Please refer to the full prescribing information of the medicinal products that are used in combination with Pegasys.When used in combination with ribavirin, please refer to the ribavirin prescribing information.

2.2.1 Standard Dosage

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

Chronic Hepatitis C– treatment-naïve patients:
The recommended dosage for Pegasys, alone or in combination with oral ribavirin, is 180 mcg once-weekly by subcutaneous administration in the abdomen or thigh. Ribavirin should be administered with food. The recommended duration of Pegasys monotherapy is 48 weeks. Please refer to the full prescribing information for ribavirin. The duration of combination therapy and the daily dose of ribavirin given in combination with Pegasys should be individualized based on the patient's viral genotype (see Table 1). The use of Pegasys monotherapy in patients with normal ALT levels at baseline have not been studied in any clinical trials.

Table 1 ***Dosing Recommendations***

Genotype	Pegasys Dose	Ribavirin Dose	Duration
Genotype 1,4*	180 mcg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotype 2,3	180 mcg	800 mg	24 weeks

*In the small number of patients infected with genotype 4 across all treatment groups in NV15942 (N=36), the sustained virological response (SVR) was highest in the group of patients treated for 48 weeks with 1000 milligrams or 1200 milligrams of ribavirin (N=9/11, 82%).

In general, patients infected with genotype 4 are considered hard to treat and limited study data (N=49) are compatible with a posology as for genotype 1. When deciding on the duration of therapy, the presence of additional risk factors should also be considered. For patients infected with genotype 5 or 6, this posology should also be considered.

Chronic hepatitis C – treatment-experienced patients:
The recommended dose of Pegasys in combination with ribavirin is 180 mcg once weekly by subcutaneous administration. For patients <75 kg and ≥75 kg, 1000 mg daily and 1200 mg daily of ribavirin, respectively, should be administered.

Patients who have detectable virus at week 12 should stop therapy. The recommended duration of therapy is up to 72 weeks in genotype 1 or 4 patients and 48 weeks in genotype 2 or 3 patients.

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

Duration of therapy when Pegasys is used in combination with other medicinal products
Please also refer to the full prescribing information of the medicinal products that are used in combination with Pegasys.

Predictability of response – 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 8).

Table 2 Predictive Value of Week 12 Virological Response at the Recommended Dosing Regimen while receiving ribavirin and peginterferon Combination Therapy

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

Patients treated with Pegasys who failed to achieve an early virological response were highly unlikely (<5%) to achieve a sustained virological response with continued therapy. In clinical studies, 97 of 102 difficult to treat patients (genotype 1) who received Pegasys and ribavirin combination therapy for 48 weeks and who failed to achieve an early virological response also failed to achieve a sustained virological response 24 weeks after therapy. This indicates a 95% negative predictability by week 12. Consideration should be given to discontinuing anti-viral therapy in these patients, especially if in a non-cirrhotic stage of disease.

The negative predictive value of week 12 virological response 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, respectively, for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Prior treatment-experienced patients
In non-responder patients re-treated for 48 (genotype 2 and 3) or 72 weeks (genotype 1 and 4), viral suppression at week 12 (undetectable HCV RNA defined as <50 IU/mL) has 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.

Discontinuation of treatment
Discontinuation of treatment is recommended if at least a 2 $\log_{10}$ reduction from baseline or undetectable HCV RNA has not been demonstrated by 12 weeks of therapy (see section Predictability of response). Additionally, if patients have not achieved undetectable HCV RNA by week 24, therapy should be discontinued.

Dose modification
General
When dose modification is required for moderate to severe adverse reactions (clinical and/or laboratory), initial dose reduction to 135 mcg is generally adequate. However, in some cases, dose reduction to 90 mcg or 45 mcg is necessary. Dose increases to or toward the original dose may be considered when the adverse reaction abates (see sections 2.4 and 2.6).

Hematological
Dose reduction is recommended if the absolute neutrophil count (ANC) is less than 750 cells/mm^3. For patients with ANC values below 500 cells/mm^3, treatment should be suspended until ANC values return to more than 1000 cells/mm^3. Therapy should initially be reinstituted at 90 mcg Pegasys and the neutrophil count monitored.

Dose reduction to 90 mcg is recommended if the platelet count is less than 50,000 cells/mm^3. Cessation of therapy is recommended if platelet count decreases to levels below 25,000 cells/mm^3.

Dose modification for ribavirin in Chronic Hepatitis C when administered in combination therapy
For management of treatment-emergent anemia, the dose of Ribavirin should be reduced to 600 mg per day (200 mg in the morning and 400 mg in the evening) if either of the following apply:

- A patient without significant cardiovascular disease experiences a fall in hemoglobin levels to <10 g/dl and ≥8.5 g/dl or
- A patient with stable cardiovascular disease experiences a fall in hemoglobin levels by ≥2 g/dl during any 4 weeks of treatment.

Ribavirin should be *discontinued* under the following circumstances:

- If a patient without significant cardiovascular disease experiences a confirmed decrease in hemoglobin levels to <8.5 g/dl.
- If a patient with stable cardiovascular disease maintains a hemoglobin value <12 g/dl despite 4 weeks on a reduced dose.

Once the patient's ribavirin dose has been withheld due to a laboratory abnormality or clinical manifestation an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily depending upon the physician's judgment. However, it is not recommended that ribavirin be increased to the original dose (1000 mg or 1200 mg).

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

Table 3 Dose Adjustment for Adverse Reaction (For further guidance see also text above)

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

2.2.2 Special Dosage Instructions

Geriatric use
No dose adjustment of Pegasys is required in patients ≥ 65 years of age
Renal impairment
No dose adjustment is required for adult patients with mild or moderate renal impairment A reduced dose of 135 mcg once weekly Pegasys is recommended in adult patients with severe renal impairment. In adult patients with end stage renal disease, a starting dose of Pegasys 135 mcg once weekly should be used (see section 3.2.5 Pharmacokinetic and Pharmacodynamics in Special Populations).

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.

No data is available for pediatric patients with renal impairment.

Hepatic impairment
Fluctuations in abnormalities of liver function tests are common in patients with chronic hepatitis. However, as with other alpha interferons, increases in ALT levels above baseline have been observed in patients treated with Pegasys, including patients with a virological response.

For HCV patients, the dose should be reduced initially to 135 mcg in the presence of progressive or persistent ALT increases above baseline values. When increase in ALT levels is progressive despite dose reduction, or is accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued (see section Special Warnings and Special Precautions).

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

2.3 Contraindications

Pegasys is contraindicated in:

- patients with known hypersensitivity to alpha interferons, to *E. coli*-derived products, to polyethyleneglycol or to any component of the product.
- patients with autoimmune hepatitis.
- patients with severe hepatic dysfunction or decompensated cirrhosis.
- neonates and infants up to 3 years of age.
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 2.4).
- Initiation of Pegasys is contraindicated in HIV-HCV patients with cirrhosis and a Child-Pugh score ≥ 6 except if only due to indirect hyperbilirubinemia caused by drugs such as atazanavir and indinavir
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorders, mainly depression.

Due to the use of ribavirin, pregnant or breast feeding women must not be exposed to Pegasys/ribavirin combination therapy (please refer to section 2.5.1 Pregnancy and 2.5.2 Nursing Mothers).

2.4 Special Warnings and Special Precautions for Use

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

Treatment with Pegasys monotherapy or Pegasys/ribavirin combination therapy should be initiated only by a physician experienced in the treatment of patients with hepatitis C and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of further therapy.

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

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

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

Pegasys or Pegasys/ribavirin treatments were associated with decreases in both total white blood cell (WBC) count and ANC, usually starting within the first 2 weeks of treatment (see section 2.6.1). In clinical studies, progressive decreases thereafter were infrequent. Dose reduction is recommended when ANC decreases to levels below 750 cells/mm^3 (see section 2.2). For patients with ANC values below 500 cells/mm^3, treatment should be suspended until ANC values return to more than 1000 cells/mm^3. In clinical trials with Pegasys or Pegasys/ribavirin, the decrease in ANC was reversible upon dose reduction or cessation of therapy.

Pegasys or Pegasys/ribavirin treatments were associated with decreases in platelet count, which returned to pretreatment (baseline) levels during the posttreatment observation period (see section 2.6). Dose reduction is recommended when platelet count decreases to levels below 50,000 cells/mm^3 and cessation of therapy is recommended when platelet count decreases to levels below 25,000 cells/mm^3 (see section 2.2).

Anemia
Anemia (hemoglobin ≤10 g/dL) was observed in 13% of patients in clinical trials treated with Pegasys/ribavirin 1000 mg or 1200 mg for 48 weeks and in 3% with Pegasys/ribavirin 800 mg for 24 weeks (see section 2.6.1 Laboratory Abnormalities). The maximum drop in hemoglobin occurred within 4 weeks of initiation of ribavirin therapy. Complete blood counts should be obtained pretreatment, at weeks 2 and 4 of therapy and periodically thereafter. If there is any deterioration of cardiovascular status, ribavirin therapy should be suspended or discontinued (see section 2.2 Dosage and Administration). Please refer also to the approved ribavirin prescribing information.
The use of Pegasys and ribavirin combination therapy in chronic hepatitis C patients who failed prior treatment, has not been adequately studied in patients who discontinued prior therapy for hematological adverse events. Physicians considering treatment in these patients should carefully weigh the risks versus the benefits of retreatment. The risk of developing anaemia is higher in the female population. Pancytopenia (marked decreases in red blood cells, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of ribavirin and azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see section 2.8).

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

Neuropsychiatric: Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including Pegasys or Pegasys/ribavirin. Depression, suicidal ideation, and suicide may occur in patients with and without previous psychiatric illness. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with interferon or Pegasys. Pegasys monotherapy and Pegasys/ribavirin combination therapy should be used with caution in patients who report a history of depression, and physicians should monitor all patients for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of Pegasys or Pegasys/ribavirin therapies, and patients should report any sign or symptom of depression immediately. In severe cases therapy should be stopped and psychiatric intervention sought (see section 2.6).

Cardiovascular: Because cardiac disease may be worsened by ribavirin-induced anemia, HCV patients with a history of significant or unstable cardiac disease should not use ribavirin. Cardiovascular events such as hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alpha interferon therapies, including Pegasys and Pegasys/ribavirin. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of 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 2.2.2 Special Dosage Instructions and refer also to the approved ribavirin prescribing information).

Hepatic function:
HCV: In patients who develop evidence of hepatic decompensation during treatment, Pegasys or Pegasys/ribavirin should be discontinued. As with other alpha interferons, increases in ALT levels above baseline have been observed in patients treated either with Pegasys or with Pegasys/ribavirin, including patients with a virological response. When the increase in ALT levels is progressive despite dose reduction or is accompanied by increased direct bilirubin, therapy should be discontinued (see section 2.2).

HBV: Unlike HCV, disease exacerbations during therapy are not uncommon and are characterized 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 case of flares exceeding 10 times the upper limit of normal, Pegasys dosing was reduced or withheld until the transaminase elevations subsided, while in the rest therapy was continued unchanged. More frequent monitoring of hepatic function was recommended in all instances.

Bone marrow suppression: Alfa-interferons suppress bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pretreatment and monitored routinely during therapy. Pegasys monotherapy or Pegasys/ribavirin combination therapy should be used with caution in patients with baseline neutrophil counts <1500 cells/mm^3, with baseline platelet count <90,000 cells/mm^3 or baseline hemoglobin <12 g/dl (see section 2.2). As with other interferons, caution should be exercised when administering Pegasys or Pegasys/ribavirin in combination with other potentially myelosuppressive agent.

Endocrine: As with other interferons, Pegasys or Pegasys/ribavirin may cause or aggravate hypothyroidism and hyperthyroidism. Discontinuation of therapy should be considered in patients whose thyroid abnormalities cannot be adequately treated. Hyperglycemia, hypoglycemia and diabetes mellitus have been observed in patients treated with alpha interferons. Patients with these conditions who cannot be effectively controlled by medication should not begin Pegasys monotherapy nor Pegasys/ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Pegasys or Pegasys/ribavirin therapies.

Autoimmune: Exacerbation of autoimmune disease has been reported in patients receiving alpha interferon therapy; Pegasys or Pegasys/ribavirin should be used with caution in patients with autoimmune disorders.

Use of alpha interferons has been associated with exacerbation or provocation of psoriasis and sarcoidosis. Pegasys alone or in combination with ribavirin must be used with caution in patients with psoriasis, and in case of appearance or worsening of psoriatic lesions, discontinuation of therapy should be considered.

Hypersensitivity: Serious, acute hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If such a reaction develops during treatment either with Pegasys or with Pegasys/ribavirin, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Pulmonary: As with other alpha interferons, pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonia, and pneumonitis, including fatality, have been reported during therapy with Pegasys alone or in combination with ribavirin. If there is evidence of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.

Ophthalmologic: As with other interferons, retinopathy including retinal hemorrhages, cotton wool spots, papilledema, optic neuropathy and retinal artery or vein obstruction, which may result in loss of vision, have been reported after treatment with peginterferon alfa-2a. All patients should have a baseline eye examination. Any patient complaining of decreased or loss of vision must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of Pegasys monotherapy or Pegasys/ribavirin combination therapy is recommended in patients with diabetes mellitus or hypertension. Pegasys or Pegasys/ribavirin should be discontinued in patients who develop new or worsening ophthalmologic disorders.

HIV-HCV Coinfection
Please refer to the respective Package Inserts 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 Tablet package insert).

Co-infected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with alpha interferous, including Pegasys, with or without ribavirin. 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 2.8).

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

Transplantation: The safety and efficacy of Pegasys and ribavirin treatment have not been established in patients with liver and other transplantations. As with other alpha interferons, liver and renal graft rejections have been reported on Pegasys, alone or in combination with ribavirin.

Colitis: Fatal and non-fatal ulcerative or hemorrhagic/ischemic colitis have been observed within 12 weeks of starting alfa interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations. Pegasys treatment should be discontinued immediately if these symptoms develop. The colitis usually resolves within 1 to 3 weeks of discontinuation of alfa interferon.

Pancreatitis: Fatal and non-fatal pancreatitis have occurred during alpha interferon and ribavirin treatment. Pegasys and ribavirin should be suspended if symptoms or signs suggestive of pancreatitis are observed. Pegasys and ribavirin should be discontinued in patients diagnosed with pancreatitis.

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.

2.4.1 Effects on Ability to Drive and Use Machines

Patients who develop dizziness, confusion, somnolence or fatigue should be cautioned to avoid driving or operating machinery.

2.4.2 Laboratory Tests

Before beginning Pegasys monotherapy or Pegasys/ribavirin combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional laboratory testing should be performed periodically during therapy.

The entrance criteria used for the clinical studies of Pegasys alone or in combination with ribavirin may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count ≥90,000/mm^3,
- Absolute neutrophil count (ANC) ≥1500 cells/mm^3,
- TSH and T_4 within normal limits or adequately controlled thyroid function.

HIV-HCV co-infection: CD4+ ≥ 200/µl or CD4+ ≥ 100/µl - < 200/µl and HIV-1 RNA < 5000 copies/mL using Amplicor HIV-1 Monitor Test, v 1.5

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility

Pegasys has not been studied for its effect on fertility. As with other alpha interferons, prolongation of the menstrual cycle accompanied by both a decrease and a delay in the peak of 17β-estradiol and progesterone levels have been observed following administration of peginterferon alfa-2a to female monkeys. A return to normal menstrual rhythm followed discontinuation of treatment.

Pegasys has not been studied for its effect on male fertility. However, treatment with interferon alfa-2a did not affect fertility of male rhesus monkeys treated for 5 months at doses up to 25 x 10^6 IU/kg/day.

Contraception

When used with ribavirin it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded.

2.5.2 Pregnancy

Pegasys is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

Pegasys has not been studied for its teratogenic effect. Treatment with interferon alfa–2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys. No teratogenic effects were seen in the offspring delivered at term. However, as with other alpha interferons, women of childbearing potential receiving Pegasys therapy should be advised to use effective contraception during therapy.

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 and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking ribavirin. Ribavirin therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

Patients on treatment with Pegasys should take effective contraceptive measures.

Please refer also to the approved ribavirin prescribing information.

Labor and Delivery

The safe use of Pegasys during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether Pegasys or ribavirin are excreted in human milk. No studies have been conducted to assess the impact of Pegasys or ribavirin on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, a decision must be made either to discontinue breast-feeding or discontinue treatment, based on the importance of the therapy to the mother.

2.5.4 Renal Impairment

No dose adjustment is required for patients with mild or moderate renal impairment. A reduced dose of 135 mcg once weekly Pegasys is recommended in patients with severe renal impairment. In patients with severe renal impairment, a starting dose of Pegasys 135 mcg once weekly should be used (see section 3.2.5). 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 *(see section 2.2.2 Special Dosage Instruction)*. Pegasys should be used with caution in patients with creatinine clearance < 50ml/min. Please refer to the approved ribavirin prescribing information for information regarding the use of ribavirin in patients with renal impairment.

2.5.5 Hepatic Impairment

In patients with compensated cirrhosis (e.g. Child Pugh A), Pegasys has been shown to be effective and safe. Pegasys has not been studied in patients with decompensated cirrhosis (e.g. Child Pugh B/C or esophageal varices) (see section 2.3).

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	1
	Grade 1-2	2
	Grade 3-4*	3
Ascites	Absent	1
	Slight	2
	Moderate	3
S-Bilirubin (mg/dl)	<2	1
	2-3	2
	>3	3
SI unit = µmol/l)	<34	1
	34-51	2
	>51	3
S-Albumin (g/dl)	>3.5	1
	3.5-2.8	2
	<2.8	3
INR	<1.7	1
	1.7-2.3	2
	>2.3	3

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

2.5.6 Pediatric Use

Safety and effectiveness have not been established in patients below the age of 18. In addition, Pegasys injectable solutions contain benzyl alcohol. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known. Therefore, Pegasys should not be used in neonates or infants (see section 2.3).

2.5.7 Geriatric Use

No special dosage modification of Pegasys is required for geriatric patients based upon pharmacokinetic, pharmacodynamic, tolerability, and safety data from clinical trials.

2.6 Undesirable effects

Experience from clinical trials

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

Chronic Hepatitis B:

In clinical trials of 48 week treatment and 24 weeks follow-up, the safety profile for Pegasys in chronic hepatitis B was similar to that seen in chronic hepatitis C, although the frequency of reported adverse reactions was notably less in CHB (see Table 5). Eighty eight (88%) percent of Pegasys-treated patients experienced adverse reactions, as compared to 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. Five percent of patients withdrew from Pegasys treatment due to adverse events or laboratory abnormalities, while less than 1% withdrew from lamivudine treatment for safety reasons. The withdrawal rates for patients with cirrhosis were similar to those of the overall population in each treatment group. The addition of lamivudine had no effect on the safety profile of Pegasys.

Chronic Hepatitis C:

In clinical trials, the incidence of withdrawal from treatment for all patients due to adverse events and laboratory abnormalities was 9% for Pegasys monotherapy and 13% for Pegasys in combination with ribavirin 1000/1200 mg given for 48 weeks. Respectively, only 1% or 3% of patients required discontinuation of either Pegasys or Pegasys/ribavirin for laboratory abnormalities. The withdrawal rates for patients with cirrhosis were similar to those of the overall population. In comparison to 48 weeks of treatment with Pegasys and ribavirin 1000/1200 mg, reducing treatment exposure to 24 weeks and daily dose of ribavirin to 800 mg resulted in a reduction in serious adverse events (11% vs 3%), premature withdrawals for safety reasons (13% vs 5%) and the need for ribavirin dose modification (39% vs 19%).

Chronic Hepatitis C prior non-responder patients

In a clinical trial which included 72 and 48 weeks treatments of prior pegylated interferon alfa-2b/ribavirin non-responder patients, the frequency of withdrawal from Pegasys treatment was 12% and ribavirin treatment was 13% due to adverse events or laboratory abnormalities, for patients in the 72-week arms. In comparison, in 48 week treatment arms, 6% withdrew from Pegasys and 7% withdrew from ribavirin treatment. Similarly for patients with cirrhosis, withdrawal rates from Pegasys and ribavirin treatment were higher in the 72-week treatment arms, (13% and 15%) compared to the 48-week arms which were (6% and 6%). Patients who withdrew from previous therapy due to hematological toxicity were excluded from enrolling in this trial.

In another clinical trial, patients with advanced fibrosis or cirrhosis (Ishak score of 3 to 6) who had not responded to previous treatment were enrolled with baseline platelet counts as low as 50,000/mm^3 and treated for 48 weeks. Due to a high prevalence of the advanced cirrhosis/fibrosis state and the low baseline platelet counts among patients in this study, the frequency of haematologic lab abnormalities in the first 20 weeks of the trial were as follows: hemoglobin <10 g/dL, 26.3%;, ANC <750/mm^3, 30%;, and platelet <50,000/ mm^3, 13% .

HIV-HCV Co-infection

In HIV-HCV co-infected patients, the clinical adverse events reported on Pegasys, alone or in combination with ribavirin, were similar to that observed in HCV mono-infected patients. Limited safety data (N= 51) is available in co-infected patients with CD4+ cell counts <200/µl. In study NR15961, the incidence of withdrawal from treatment for clinical adverse events, laboratory abnormalities or AIDS-defining events was 16% for Pegasys monotherapy, and 15% for Pegasys in combination with ribavirin 800 mg, given for 48 weeks. Respectively, 4% or 3% of patients required discontinuation of Pegasys or Pegasys/ribavirin for laboratory abnormalities. In combination therapy, Pegasys dose modification occurred in 39%, and ribavirin dose modification occurred in 37%, of the co-infected patients. Serious adverse events were reported in 21% and 17% of those receiving Pegasys monotherapy or in combination with ribavirin, respectively.

Pegasys containing treatment was associated with an on-treatment reduction in absolute CD4+ cell count without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. Pegasys containing treatment had no apparent negative impact on the control of HIV viremia during therapy or follow-up

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

Table 4 Safety Overview of Pegasys Treatment Regimens-Combination Therapy with Ribavirin for HCV and HIV-HCV Patients

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

Table 5 shows those adverse reactions occurring in ≥ 10% of patients who have received Pegasys, Pegasys plus ribavirin or interferon alfa-2b plus ribavirin in different indications.

Table 5 Undesirable Effects (≥ 10% Incidence in Any Treatment Group) for HBV or HCV Patients

	HBV	**HCV**				
Body System	**Pegasys*** 180 mcg 48 weeks N=448	**HCV Pegasys** 180 mcg 48 weeks N=827	**HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 24 weeks N=207	**HCV Pegasys** 180 mcg & **Ribavirin** 1000/ 1200 mg 48 weeks N=887	**HCV IFN alfa-2b 3 MIU & Ribavirin** 1000/ 1200 mg 48 weeks N=443	**HIV-HCV Pegasys** 180 mcg & **Ribavirin** 800 mg 48 weeks N=288
	%	%	%	%	%	%
Metabolism & Nutrition						
Anorexia	13	16	20	27	26	23
Weight Decrease	4	5	2	7	10	16
Neuro/Psych Disorders						
Headache	23	52	48	47	49	35
Insomnia	6	20	30	32	37	19
Irritability	3	17	28	24	27	15
Depression	4	18	17	21	28	22
Dizziness	6	14	13	15	14	7
Concentration Impairment	2	9	8	10	13	2
Anxiety	3	6	8	8	12	8
Respiratory Disorder						
Dyspnoea	1	5	11	13	14	7
Cough	2	4	8	13	7	3
Gastro-intestinal Disorders						
Nausea	6	24	29	28	28	24
Diarrhoea	6	16	15	14	10	16
Abdominal Pain	4	15	9	10	9	7
Skin						
Alopecia	17	22	25	24	33	10
Pruritus	6	12	25	21	18	5
Dermatitis	<1	9	15	16	13	1
Dry skin	1	5	13	12	13	4
Musculo-skeletal						
Myalgia	25	37	42	38	49	32
Arthralgia	10	26	20	22	23	16
General						
Fatigue	21	49	45	49	53	40
Pyrexia	52	35	37	39	54	41
Rigors	6	30	30	25	34	16
Injection-Site Reaction	7	22	28	21	15	10
Asthenia	11	7	18	15	16	26
Pain	1	11	9	10	9	6

*In clinical trials, 450 patients received Pegasys in combination with lamivudine. The addition of lamivudine had no effect on the safety profile of Pegasys.

Table 6 Adverse Reactions occurring in ≥ 10% of Hepatitis C patients with normal ALT levels

	PEGASYS 180 mcg with ribavirin 800 mg 24 weeks	**PEGASYS 180 mcg with ribavirin 800 mg 48 weeks**	**Untreated Control 48 weeks**
	(n=212)	**(n=210)**	**(n=69)**
	%	**%**	**%**
General disorders			
Fatigue	51	51	17
Pyrexia	30	43	3
Rigors	24	25	1
Asthenia	22	23	10
Injection site reaction	16	16	-
Decreased appetite	8	16	1
Back pain	9	10	9
Psychiatric disorders			
Insomnia	35	36	7
Depression	26	27	6
Irritability	27	26	1
Anxiety	10	8	3
Musculoskeletal, connective tissue and bone disorders			
Myalgia	38	44	7
Arthralgia	32	30	4
Nervous system disorders			
Headache	44	56	7
Dizziness	89	17	1
Skin and subcutaneous tissue disorders			
Alopecia	20	28	-
Pruritus	16	20	1
Rash	14	16	-
Dermatitis			
Dry skin	11	9	-
Gastrointestinal disorders			
Nausea	32	40	1
Diarrhoea	19	26	4
Vomiting	12	13	3
Upper abdominal pain	9	12	7
Dyspepsia	9	10	-
Respiratory, thoracic and mediastinal disorders			
Cough	14	19	1
Dyspnoea	14	15	-
Pharyngitis	9	10	4
Metabolism and nutrition disorders			
Anorexia	16	13	1

Adverse reactions reported in ≥1% but <10% on Pegasys/ribavirin combination or Pegasys monotherapy in HBV, HCV and HIV-HCV patients were:

Infections and Infestations: herpes simplex, URI infection, bronchitis, oral candidiasis

Blood and the lymphatic system disorders: lymphadenopathy, anemia, thrombocytopenia

Endocrine disorders: hypothyroidism, hyperthyroidism

Neuropsychiatric disorders: memory impairment, taste disturbance, paraesthesia, hypoesthesia, tremor, weakness, emotional disorders, mood alteration, nervousness, aggression, libido decreased, migraine, somnolence, hyperesthesia, nightmares, syncope

Eye disorders: vision blurred, xerophthalmia, eye inflammation, eye pain

Ear and labyrinth disorders: vertigo, earache

Cardiac disorders: palpitations, edema peripheral, tachycardia

Vascular disorders: flushing

Respiratory, thoracic and mediastinal disorders: sore throat, rhinitis, nasopharyngitis, sinus congestion, dyspnea exertional, epistaxis

Gastrointestinal disorders: vomiting, dyspepsia, flatulence, dry mouth, mouth ulceration, gingival bleeding, stomatitis, dysphagia, glossitis

Skin and subcutaneous tissue disorders: skin disorder, rash, eczema, psoriasis, urticaria, photosensitivity reaction, sweating increased, night sweats

Musculoskeletal, connective tissue and bone disorders: bone pain, back pain, neck pain, muscle cramps, muscle weakness, musculoskeletal pain, arthritis

Reproductive system and breast disorders: impotence

General disorders and administration site conditions: influenza-like illness, malaise, lethargy, hot flushes, chest pain, thirst

Other adverse reactions reported in ≥ 1% to ≤ 2% of HIV-HCV patients receiving Pegasys/ribavirin combination included: hyperlactacidemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

As with other alpha interferon therapies, uncommon to rare cases of the following serious adverse events have been reported in patients receiving Pegasys/ribavirin combination or Pegasys monotherapy during clinical trials: lower respiratory tract infection, skin infection, otitis externa, endocarditis, suicide, substance overdose, hepatic dysfunction, fatty liver, cholangitis, malignant hepatic neoplasm, peptic ulcer, gastrointestinal bleeding, pancreatitis, arrhythmia, atrial fibrillation, pericarditis, autoimmune phenomena (e.g., ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE), myositis, peripheral neuropathy, sarcoidosis, interstitial pneumonitis with fatal outcome, pulmonary embolism, corneal ulcer, coma, cerebral hemorrhage, TTP, psychotic disorder, and hallucination.

Based on cumulative data set, rarely, alpha interferon including Pegasys, used alone or in combination with ribavirin, may be associated with pancytopenia, and very rarely, aplastic anemia has been reported.

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

2.6.1 Laboratory Abnormalities

For combination therapy in HCV patients, please refer also to the approved ribavirin prescribing information for the effects of ribavirin on laboratory parameters.

Hematology: as with other interferons, treatment with either Pegasys or Pegasys/ribavirin was associated with decreases in hematological values, which generally improved with dosage modification and returned to pretreatment levels within 4 to 8 weeks upon cessation of therapy (see sections 2.2 and 2.4). Although hematological toxicities of neutropenia, thrombocytopenia and anemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment.

Hemoglobin and hematocrit: although treatment with Pegasys monotherapy was associated with small gradual decreases in hemoglobin and hematocrit, less than 1% of all patients, including those with cirrhosis, required dose modification for anemia. Approximately 10% of patients on 48 weeks Pegasys/ribavirin 1000/1200 mg combination therapy required dose modification for anemia. Anemia (hemoglobin < 10g/dL) was reported in 7% and 14% of HIV-HCV co-infected patients treated with Pegasys monotherapy or in combination with ribavirin, respectively.

White blood cells: Pegasys treatment was associated with decreases in values for both total WBC count and ANC. Approximately 4% of HBV or HCV patients receiving Pegasys and 5% of HCV patients receiving Pegasys/ribavirin had transient decreases in ANC to levels below 500 cells/mm^3 at some time during therapy. In HIV-HCV co-infected patients, 13% and 11% of those receiving Pegasys monotherapy and combination therapy, respectively, had decreases in ANC levels below 500 cells/mm^3.

Platelet count: Pegasys treatment was associated with decreases in values for platelet counts. In clinical trials, approximately 5% of patients had decreases in platelet counts to levels below 50,000/mm^3, mostly in patients with cirrhosis and who entered the study with baseline platelet counts as low as 75,000/mm^3. In clinical trials for hepatitis B, 14% of patients had decreases in platelet counts to below 50,000/mm^3, mostly in patients who entered the study with low baseline platelet counts. In HIV-HCV patients, 10% and 8% of those receiving Pegasys monotherapy and combination therapy, respectively, had decreases in platelets below 50,000/mm^3 .

Thyroid function: Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see section 2.4). The frequencies observed with Pegasys were similar to those observed with other interferons.

Triglycerides: triglyceride levels are found to be elevated in patients receiving alpha interferon therapy, including Pegasys.

Anti-interferon Antibodies: three percent of HCV patients (25/835) receiving Pegasys with or without ribavirin developed low-titer neutralizing anti-interferon antibodies. The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed.

Laboratory values for HIV-HCV co-infected patients

Although hematological toxicities of neutropenia, thrombocytopenia and anemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment. Decrease in ANC levels below 500 cells/mm3 was observed in 13% and 11% of patients receiving Pegasys monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm3 was observed in 10% and 8% of patients receiving Pegasys monotherapy and combination therapy, respectively. Anemia (hemoglobin < 10g/dL) was reported in 7% and 14% of patients treated with Pegasys monotherapy or in combination therapy, respectively.

2.6.2 Post Marketing Experience

During the post-marketing period, erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis, pure red cell aplasia (PRCA) and homicidal ideation have been reported very rarely with combination therapy of Pegasys and ribavirin.

Dehydration has been reported rarely with combination therapy of Pegasys and ribavirin .

As with other alpha interferons, serous retinal detachment has been reported with Pegasys and ribavirin combination therapy

As with other alpha interferons, liver and renal graft rejections have been reported for Pegasys, alone or in combination with ribavirin.

Adverse reactions reported in a post-marketing setting are: tongue pigmentation.

Facial palsy has been reported with Pegasys.

Respiratory, thoracic and mediastinal disorders: Pulmonary arterial hypertension (Frequency unknown).

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.

2.7 Overdose

Overdoses with Pegasys involving at least two injections on consecutive days (instead of weekly interval) up to daily injections for one week (i.e. 1260mcg/week) have been reported. None of these patients experienced unusual, serious or treatment-limiting events. Weekly doses of up to 540 mcg and 630 mcg have been administered in renal cell carcinoma and chronic myelogenous leukemia clinical trials, respectively. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia consistent with interferon therapy. No cases of overdose of ribavirin have been reported in clinical trials.

Please refer to the approved ribavirin prescribing information.

2.8 Interactions with other Medical Products and other Forms of Interaction

No pharmacokinetic interactions between Pegasys and ribavirin have been observed in HCV clinical trials in which Pegasys was used in combination with ribavirin. Similarly, lamivudine had no effect on Pegasys pharmacokinetics in HBV clinical trials in which Pegasys was used in combination with lamivudine.

Treatment with Pegasys 180 mcg once weekly for 4 weeks had no effect on the pharmacokinetics profiles of tolbutamide (CYP 2C9), mephenytoin (CYP 2C19), debrisoquine (CYP 2D6), and dapsone (CYP 3A4) in healthy male subjects. Pegasys is a modest inhibitor of cytochrome P450 1A2 as a 25% increase in theophylline's AUC was observed in the same study. Comparable effects on theophylline's pharmacokinetics have been seen after treatment with standard alpha interferons. Alpha interferons have been shown to affect the oxidative metabolism of some drugs by reducing the activity of hepatic microsomal cytochrome P450 enzymes. Theophylline serum concentrations should be monitored and appropriate dose adjustments of theophylline made for patients taking theophylline and Pegasys or Pegasys/ribavirin therapy concomitantly.

In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95mg; range 30mg to 150mg), treatment with PEGASYS 180µg 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.

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

Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure, as well as, peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported with use of ribavirin.

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia. Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

A non-Roche clinical trial investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that the combination is associated with an increased risk for developing peripheral neuropathy. The mechanism behind these events is not known. Such an increased risk can not be excluded for other interferons (pegylated or standard). Moreover, the benefit of the combination of telbivudine with interferon alfa (pegylated or standard) is not currently established.

Azathioprine: 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 azathioprine should be avoided.

In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close hematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped (see section 2.4).

3. PHARMACOLOGICAL PROPERTIES & EFFECTS

3.1 Pharmacodynamic Properties

Please refer to the approved ribavirin prescribing information for pharmacodynamic properties of ribavirin.

General

The conjugation of PEG reagent (bis-monomethoxypolyethylene glycol) to interferon alfa-2a forms a pegylated interferon alfa-2a (Pegasys). Interferon alfa-2a is produced biosynthetically using recombinant DNA technology, and is the product of a cloned human leukocyte interferon gene inserted into and expressed in *E. coli*. The structure of the PEG moiety directly affects the clinical pharmacology of Pegasys. Specifically, the size and branching of the 40 kDa PEG moiety define the absorption, distribution and elimination characteristics of Pegasys.

3.1.1 Mechanism of Action

Pegasys possesses the in-vitro antiviral and antiproliferative activities of interferon alfa-2a. Interferons bind to specific receptors on the cell surface initiating a complex intracellular signaling pathway and rapid activation of gene transcription. Interferon-stimulated genes modulate many biological effects including the inhibition of viral replication in infected cells, inhibition of cell proliferation and immunomodulation.

HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C who have received Pegasys. The first phase of decline occurs within 24 to 36 hours after the first dose of Pegasys and the second phase of decline occurs over the next 4 to 16 weeks in patients who achieve a sustained response. Pegasys 180 mcg per week enhances the virion clearance and improves the virological end of treatment responses compared to treatment with standard alpha interferons. Ribavirin had no significant effect on the initial viral kinetics over the first 4 to 6 weeks in patients treated with the combination of pegylated interferon alfa-2a and ribavirin or interferon alfa.

Pegasys stimulates the production of effector proteins such as serum neopterin and 2',5'-oligoadenylate synthetase in a dose-dependent manner. The stimulation of 2',5'-oligoadenylate synthetase is maximal after single doses of 135 to 180mcg Pegasys and stays maximal throughout the one-week dosing interval. The magnitude and duration of Pegasys induced 2',5'-oligoadenylate synthetase activity were reduced in subjects older than 62 years and in subjects with significant renal impairment (creatinine clearances of 20 to 40 ml/min). The clinical relevance of these findings with pharmacodynamic markers of Pegasys is not known.

3.1.2 Efficacy / Clinical Studies

Hepatitis B:

Clinical studies have demonstrated that Pegasys monotherapy is effective in the treatment of patients with chronic hepatitis B, both in patients who are HBeAg-positive and in patients who are HBeAg-negative/anti-HBe-positive.

Confirmatory clinical trials

All clinical trials recruited patients with chronic hepatitis B who had active viral replication measured by HBV DNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. Study WV16240 recruited patients who were positive for HBeAg, while study WV16241 recruited patients who were negative for HBeAg and positive for anti-HBe. In both studies the treatment duration was 48 weeks, with 24 weeks of treatment-free follow-up. Both studies compared Pegasys plus placebo vs Pegasys plus lamivudine vs lamivudine alone. No HBV-HIV co-infected patients were included in these clinical trials. Response rates at the end of follow-up for the two studies are presented in Table 7. HBV DNA was measured by the COBAS AMPLICOR HBV MONITOR Assay (limit of detection 200 copies/ml).

Table 7 Serological, Virological and Biochemical Responses in Chronic Hepatitis B

	HBeAg positive Study WV16240			**HBeAg negative / anti-HBe positive Study WV16241**		
	Pegasys 180mcg & **Placebo** (N= 271)	**Pegasys** 180mcg & **Lamivudine** 100mg (N=271)	**Lamivudine** 100mg (N=272)	**Pegasys** 180mcg & **Placebo** (N=177)	**Pegasys** 180mcg & **Lamivudine** 100mg (N=179)	**Lamivudine** 100mg (N=181)
HBeAg Sero-conversion	32%[1]	27%	19%	N/A	N/A	N/A
HBV DNA*	32%[2]	34%	22%	43%[5]	44%	29%
ALT Normalization	41%[3]	39%	28%	59%[6]	60%	44%
HBsAg Sero-conversion	3%[4]	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 x 10^4 copies/ml

[1] Odds Ratio (95% CI) vs lamivudine = 2.00 (1.34 – 2.97)
p-value (stratified Cochran-Mantel-Haenszel test) < 0.001

[2] Odds Ratio (95% CI) vs lamivudine = 1.64 (1.12 – 2.42)
p-value (stratified Cochran-Mantel-Haenszel test) = 0.012

[3] Odds Ratio (95% CI) vs lamivudine = 1.77 (1.23 – 2.54)
p-value (stratified Cochran-Mantel-Haenszel test) = 0.002

[4] Odds Ratio not definable
p-value (stratified Cochran-Mantel-Haenszel test) = 0.004

[5] Odds Ratio (95% CI) vs lamivudine = 1.84 (1.17 – 2.89)
p-value (stratified Cochran-Mantel-Haenszel test) = 0.007

[6] Odds Ratio (95% CI) vs lamivudine = 1.86 (1.22 – 2.85)
p-value (stratified Cochran-Mantel-Haenszel test) = 0.004

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 normalization 12 months after end of treatment were 42% (41/97) and 59% (58/99), respectively.

Chronic Hepatitis C:

Clinical studies have demonstrated that Pegasys alone or in combination with ribavirin is effective in the treatment of patients with chronic hepatitis C, including cirrhotic patients with compensated liver disease.

Clinical Trial Results

Predictability of response

Patients demonstrating an early virological response by week 12 (86% of total patients treated) have an increased probability of achieving a sustained virological response with a full course of therapy. An early virological response is defined as unquantifiable levels of HCV RNA or at least a 99% reduction (2 log drop) in viral titre from baseline by week 12 of therapy. In clinical trials, 66% of patients experiencing an early virological response went on to achieve a sustained virological response.

Pegasys monotherapy

In three randomised studies, altogether 701 adult, interferon-naïve patients with a diagnosis of chronic hepatitis C were treated at the recommended monotherapy dose of 180 micrograms Pegasys. An additional study specifically recruited patients with a histological diagnosis of cirrhosis or transition to cirrhosis and 87 patients were treated with Pegasys 180 micrograms per week. About 80% of the patients in this study had compensated cirrhosis (i.e., Child-Pugh A). In all studies, patients were treated for 48 weeks followed by an observation period of 24 weeks.

The virological responses for Pegasys and interferon alfa-2a are summarised in Table 8. Superior efficacy of Pegasys compared to interferon alfa-2a was demonstrated also in terms of histological response, including patients without sustained viral response and patients with cirrhosis.

Confirmatory clinical trials in treatment-naive patients

All clinical trials recruited interferon-naïve patients with chronic hepatitis C confirmed by detectable levels of serum HCV RNA, elevated levels of ALT (with the exception of study NR16071) and a liver biopsy consistent with chronic hepatitis. Study NV15495 specifically recruited patients with a histological diagnosis of cirrhosis (about 80%) or transition to cirrhosis (about 20%). Only HIV-HCV co-infected patients were included in the study NR15961 (see Table 10). These patients had stable HIV disease and mean CD4 T-cell count was about 500 cells/µl. Clinical trials in non-responders and in relapsers are in progress.

For HCV monoinfected patients and HIV-HCV co-infected patients , for treatment regimens, duration of therapy and study outcome see Tables 8, 9, 10 and Table 16, 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 8 Virological Response in HCV Patients

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

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

The virological responses of patients treated with Pegasys monotherapy and with Pegasys and ribavirin combination therapy in relation to genotype and viral load are summarised in Tables 9 and 10 for HCV monoinfected patients and HIV-HCV co-infected patients, respectively. The results of study NV15942 provide the rationale for recommending treatment regimens based on genotype (see Table 1).

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

Table 9 Sustained Virological Response Based on Genotype and Viral Load after Pegasys Combination Therapy with Ribavirin in HCV Patients

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

* Pegasys 180 mcg ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg ribavirin 800 mg, 48 w: Odds Ratio (95% CI) = 1.52 (1.07 to 2.17) P-value (stratified Cochran-Mantel-Haenszel test) = 0.020
* Pegasys 180 mcg ribavirin 1000/1200 mg, 48 w *vs.* Pegasys 180 mcg ribavirin 1000/1200 mg, 24 w: Odds Ratio (95% CI) = 2.12 (1.30 to 3.46) P-value (stratified Cochran-Mantel-Haenszel test) = 0.002.

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 10).

Table 10 Sustained Virological Response Based on Rapid Viral Response at week 4 for Genotype 1 and 4 after Pegasys Combination Therapy with Ribavirin in HCV Patients

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

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

Although limited, data indicated that shortening treatment to 24 weeks might be associated with a higher risk of relapse (see Table 11).

Table 11 Relapse of Virological Response at the End of Treatment for Rapid Virological Response Population

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

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on a sustained virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 12).

In study NV17317 in patients infected with viral genotype 2 or 3, all patients received Pegasys 180 µg sc qw and a ribavirin dose of 800 mg and were randomized 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 12)

Table 12 Sustained Virological Response Overall and Based on Rapid Viral Response by Week 4 for Genotype 2 or 3 after Pegasys Combination Therapy with Ribavirin in HCV Patients

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

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

The data indicated that shortening treatment to 16 weeks is associated with a higher risk of relapse (see Table 13).

Table 13 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.

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 randomized to four different treatments:

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

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

Multiple regression and pooled group analyses evaluating the influence of treatment duration and use of induction dosing clearly identified treatment duration for 72 weeks as the primary driver for achieving a sustained virological response. Differences in sustained virological response (SVR) based on treatment duration, demographics and best responses to previous treatment are displayed in Table 14.

Table 14 Week 12 Virological Response (VR) and Sustained Virological Response (SVR) in Patients with Virological Response at Week 12 after Treatment with Pegasys and Ribavirin Combination Therapy in Nonresponders to Peginterferon alfa-2b plus Ribavirin.

	Pegasys 360/180 or 180 µg & Ribavirin 1000/1200 mg 72 or 48 Weeks (N = 942) Pts with VR at Wk 12 [a] (N = 876)	**Pegasys 360/180 or 180 µg & Ribavirin 1000/1200 mg 72 Weeks (N = 473) SVR in Pts with VR at Wk 12 [b] (N = 100)**	**Pegasys 360/180 or 180 µg & Ribavirin 1000/1200 mg 48 Weeks (N = 469) SVR in Pts with VR at Wk 12 [b] (N = 57)**
Overall	**18% (157/876)**	**57% (57/100)**	**35% (20/57)**
Low viral load	**35% (56/159)**	**63% (22/35)**	**38% (8/21)**
High viral load	**14% (97/686)**	**54% (34/63)**	**32% (11/34)**
Genotype 1/4	**17% (140/846)**	**55% (52/94)**	**35% (16/46)**
Low viral load	**35% (54/154)**	**63% (22/35)**	**37% (7/19)**
High viral load	**13% (84/663)**	**52% (30/58)**	**35% (9/26)**
Genotype 2/3	**58% (15/26)**	**(4/5)**	**(3/10)**
Low viral load	**(2/5)**	**—**	**(1/2)**
High viral load	**(11/19)**	**(3/4)**	**(1/7)**
Cirrhosis Status			
Cirrhosis	**8% (19/239)**	**(6/13)**	**(3/6)**
Noncirrhosis	**22% (137/633)**	**59% (51/87)**	**34% (17/50)**
Best Response during Previous Treatment			
≥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 nonresponders

In the HALT-C study, patients with chronic hepatitis C and advanced fibrosis or cirrhosis who were non-responders to previous treatment with interferon alfa or pegylated interferon alfa monotherapy or in combination therapy with ribavirin were treated with Pegasys 180 mcg/week and ribavirin 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on Pegasys plus ribavirin combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. The probability for sustained virological response varied depending upon the previous treatment regimen; see Table 15.

Table 15 Sustained Virological Response in HALT-C by Previous Treatment Regimen in Non-responder Population

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

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

HIV-HCV co-infected patients

Table 16 Sustained Virological Response based on Genotype and Viral Load after Pegasys Combination Therapy with Ribavirin in HIV-HCV Co-infected Patients

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

* Pegasys 180 mcg ribavirin 800mg vs. Interferon alfa-2a 3MIU ribavirin 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001
* Pegasys 180 mcg ribavirin 800mg vs. Pegasys 180µg: Odds Ratio (95% CI) = 2.89 (1.93 to 4.32), ….P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001
* Interferon alfa-2a 3MIU ribavirin 800mg vs. Pegasys 180mcg: Odds Ratio (95% CI) = 0.53 (0.33 to 0.85), …P-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

HCV patients with normal ALT

In study NR16071, HCV patients with normal ALT values were randomized to receive peginterferon alfa-2a 180 micrograms/week with a ribavirin dose of 800 milligrams/day for either 24 or 48 weeks regardless of HCV genotype, followed by a 24 week treatment free follow-up period or an untreated control group for 72 weeks. (see Table 9 and Table 17 for the SVRs reported in the treatment arms of this study as compared to corresponding treatment arms from study NV15942).

Table 17 Sustained Virological Response based on Genotype and Viral Load after Pegasys Combination Therapy with Ribavirin in HCV Patients with Normal ALT Levels

	Pegasys 180 mcg & Ribavirin 800 mg 24 weeks	**Pegasys 180 mcg & Ribavirin 800 mg** 48 weeks
All patients	30% (63/212)	52% (109/210)
Genotype 1	13% (19/144)	40% (57/141)
Low viral load	16% (14/87)	47% (42/89)
High viral load	9% (5/55)	27% (14/51)
Genotype 2-3	72% (42/58)	78% (46/59)
Low viral load	80% (24/30)	81% (25/31)
High viral load	64% (18/25)	75% (21/38)

There were no actual studies conducted in patients with normal ALT values using ribavirin dose of 1000 or 1200 milligrams/day.

3.2 Pharmacokinetic Properties

The pharmacokinetics of Pegasys were studied in healthy volunteers and hepatitis C virus infected patients (see Table 18). The results for patients with chronic hepatitis B were similar to those for patients with chronic hepatitis C.

3.2.1 Absorption

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

3.2.2 Distribution

The volume of distribution at steady-state (V_{ss}) is 6 to 14 liters after intravenous dosing. Based on studies in rats, the drug is distributed to the liver, kidney, and bone marrow as well as being highly concentrated in the blood.

3.2.3 Metabolism

Metabolism is the main clearance mechanism for Pegasys. The metabolic profile of Pegasys is not fully characterized. In humans the systemic clearance of Pegasys is about 100 ml/h, which is 100-fold lower than that of the native interferon alfa-2a. Studies in rats indicate the metabolic products of Pegasys are excreted in the urine and to a lesser degree in the bile. The kidneys eliminate less than 10% of a dose as the intact peginterferon alfa-2a. While the PEG moiety remains attached to the interferon alfa-2a, both the PEG and the interferon alfa-2a are metabolized.

3.2.4 Elimination

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

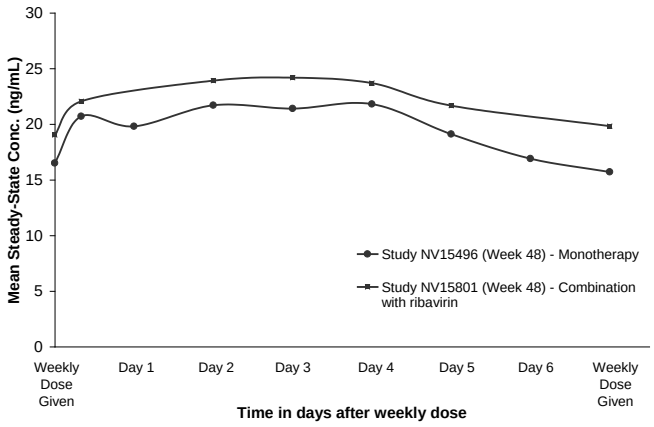
Dose-proportional increases in AUC and C_{max} are seen in healthy subjects and patients with chronic hepatitis C after once-weekly doses of Pegasys. The pharmacokinetic parameters of Pegasys are given in Table 18 for healthy subjects receiving a single subcutaneous injection of 180 mcg of Pegasys and for patients with chronic hepatitis C receiving 48 weeks of 180 mcg of Pegasys once-weekly.

Table 18 12. *Pharmacokinetic Parameters of Pegasys After Single and Multiple Dose of 180 mcg*

	Healthy Subjects 180mcg sc (N=50)	**CHC Patients in NV15496 180mcg sc Treatment (N=16)**	
Pegasys Pharmacokinetic Parameter	**Single Dose Mean ± SD [Range]**	**Single Dose Mean ± SD [Range]**	**Week 48 Dose Mean ± SD [Range]**
C_{max} (ng/ml)	14 ± 5 [6-26]	15 ± 4 [7-23]	26 ± 9 [10-40]
T_{max} (h)	92 ± 27 [48-168]	80 ± 28 [23-119]	45 ± 36 [0-97]
$AUC_{1\text{-}168\ h}$ (ng·h/ml)	1725 ±586 [524-3013]	1820 ± 586 [846-2609]	3334 ± 994 [1265-4824]
Clearance/F (ml/h)	94 ± 56 [34-337]	83 ± 50 [33-186]	60 ± 25 [37-142]
Week 48 Trough Concentration (ng/ml)	Not applicable	Not applicable	16± 6 [4-28]
Peak to Trough Ratio for Week 48	Not applicable	Not applicable	1.7 ± 0.4 [1.1-2.5]
Accumulation ($AUC_{Week\ 48}$/ $AUC_{Single\ Dose}$)	Not applicable	Not applicable	2.3 ± 1.0 [1.1-4.0]

In patients with chronic hepatitis C, steady state serum concentrations increase 2 to 3-fold compared with single-dose values and reach steady state within 5 to 8 weeks of once-weekly dosing. Once steady state has been achieved there is no accumulation of peginterferon alfa- 2a. The peak to trough ratio after 48 weeks of treatment is about 1.5 to 2.0. Peginterferon alfa-2a serum concentrations are sustained throughout 1 full week (168 hours). [Figure 1]

Figure 1. Mean Steady-State PEG-IFN alfa-2a concentrations in Patients with CHC following 180 mcg Pegasys monotherapy (NV15496) and in combination with ribavirin (NV15801)



3.2.5 Pharmacokinetics and Pharmacodynamics in Special Populations

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 18 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. Despite the lower plasma peginterferon alfa-2a exposure, patients with ESRD experienced the highest frequency of serious adverse events among the other groups in the study, likely owing to the severity and complexity of comorbidities in this patient population.

Gender

The pharmacokinetics of Pegasys were comparable between male and female healthy subjects.

Elderly

The AUC was modestly increased in subjects older than 62 years taking 180mcg Pegasys, but peak concentrations were similar in those older and younger than 62 years. Based on drug exposure, pharmacodynamic response, and tolerability, a lower starting dose of Pegasys is not needed in the geriatric patient (see section 2.5).

Non-cirrhotic and cirrhotic patients

The pharmacokinetics of Pegasys were similar between healthy subjects and patients with chronic hepatitis B or chronic hepatitis C. Comparable exposure and pharmacokinetic profiles were seen in patients with cirrhosis with compensated liver disease and patients without cirrhosis.

Site of Administration

Subcutaneous administration of Pegasys should be limited to 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.

3.3 Non clinical Safety

The nonclinical 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 alfa-2a dosed animals were similar in nature to those produced by interferon alfa-2a.

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

Pegasys plus ribavirin

When used in combination with ribavirin, Pegasys did not cause any effects in monkeys not previously seen with either active substance alone. The major treatment-related change was reversible mild to moderate anemia, the severity of which was greater than that produced by either active substance alone.

3.3.1 Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of Pegasys.

3.3.2 Genotoxicity

Pegasys was neither mutagenic nor clastogenic when tested in the Ames bacterial mutagenicity assay and in the in vitro chromosomal aberration assay in human lymphocytes, either in the presence or absence of metabolic activation. Please refer also to the approved ribavirin prescribing information.

3.3.3 Impairment of Fertility

Reproductive toxicity studies have not been performed with Pegasys. As with other alpha interferons, prolongation of the menstrual cycle was observed following administration of peginterferon alfa-2a to female monkeys.

3.3.4 Reproductive toxicity

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

4 PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid, water for injection.

4.2 Incompatibilities

It is inappropriate to mix Pegasys with other products.

4.3 Special Precautions for Storage

Store in the refrigerator at 2- 8°C. Do not freeze or shake. Store in the original package in order to protect from light.

4.4 Stability

This medicine should not be used after the expiry date (EXP) shown on the pack.

4.5 Instructions for Use, Handling and Disposal

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

Use a sterile needle and syringe to prepare Pegasys.

Disposal of syringes/sharps

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider.

For home use, a puncture resistant container for the disposal of used syringes and needles should be supplied to the patients. Patients should be thoroughly instructed in the importance of proper disposal and caution against any reuse of any needles and syringes. The full container should be disposed of according to the directions provided by the physician.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems" if available in your location.

5 PACKS

Pre-filled syringes 135 mcg	1, 4
Pre-filled syringes 180 mcg	1, 4

Medicine: keep out of reach of children

Current at Dec 2021

By Product Owner: F. Hoffmann-La Roche Ltd, Basel, Switzerland