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 pre-filled syringes. The solution is clear and colourless to light yellow.

- 180 mcg Pegasys Pre-Filled Syringe: each single use syringe contains 0.5 mL with 180 mcg peginterferon alfa-2a.
- 135 mcg Pegasys Pre-Filled Syringe: each single use syringe contains 0.5 mL with 135 mcg 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.

Other excipients: Sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, acetic acid, water for injections.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

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

Chronic Hepatitis C: Pegasys, as part of a combination regimen with other hepatitis C virus (HCV) antiviral drugs, is indicated for the treatment of adults with chronic hepatitis C (CHC) with compensated liver disease. This includes patients with or without liver cirrhosis, treatment-naive patients, patients who have failed previous treatment and patients co-infected with clinically stable HIV. The combination regimen with other hepatitis C virus (HCV) antiviral drugs should be in accordance with current treatment guidelines.

For hepatitis C virus (HCV) genotype specific treatment see section 2.2.Dosage and Administration.

2.2 Dosage and 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.

Pegasys, alone or in combination with other medicinal products, is given once weekly by subcutaneous administration in the abdomen or thigh. When used in combination with ribavirin, please refer to the ribavirin prescribing information.

Chronic Hepatitis B

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

Chronic Hepatitis C

Adult patients taking Pegasys 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.

Adult patients taking Pegasys alone or in combination with ribavirin

The recommended dosage of Pegasys, alone or in combination with ribavirin, is 180 mcg once-weekly by subcutaneous administration in the abdomen or thigh. The recommended duration of Pegasys monotherapy is 48 weeks. Please refer to the full prescribing information for ribavirin.

The duration of combination therapy with ribavirin for CHC depends on viral genotype. Ribavirin should be administered with food.

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. 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 (see table 1 and section 3.1.2).

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 16 weeks may be considered in selected patients infected with genotype 2 or 3 with LVL at baseline who become HCV negative by week 4 of treatment. Overall 16 weeks of treatment may be associated with a higher risk of relapse than a 24 week treatment duration (see section 3.1.2). 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 treatment duration. Shortening the treatment duration in patients infected with genotype 2 or 3 with HVL at baseline who become HCV negative by week 4 should be considered with more caution as this may significantly negatively impact the sustained virological response (see section 3.1.2).

Available data for patients infected with genotype 5 or 6 are limited; therefore combination treatment with 1000/1200 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 = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 4 with RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	180 micrograms	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 2 or 3 LVL with RVR**	180 micrograms	800 mg	16 weeks or 24 weeks
Genotype 2 or 3 HVL with RVR**	180 micrograms	800 mg	24 weeks
Genotype 2/3 without 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

Chronic Hepatitis C prior treatment failures

The recommended dosage of Pegasys in combination with ribavirin is 180 mcg once weekly by subcutaneous administration in the abdomen or thigh. Ribavirin should be administered with food. For patients <75 kg and ≥75 kg, 1000 mg and 1200 mg of ribavirin respectively, should be administered. The recommended duration of therapy is 72 weeks in genotype 1 or 4 patients and 48 weeks in genotype 2 or 3 patients.

HIV-HCV Co-infection

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

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 Table 2).

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 of week 12 virological response for sustained response in HCV patients treated with Pegasys 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 % or 98 %, respectively). Positive predictive values of 45% and 70% were observed, respectively, for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving combination therapy.

Prior non-responder patients

In non-responder patients retreated for 48 (genotype 2 and 3) or 72 weeks (genotype 1 and 4), viral suppression at week 12 (undetectable HCV RNA defined as HCV RNA <50 IU/mL) has shown to be predictive for sustained virological response. The negative predictive value of viral suppression at week 12 for 48 and 72 weeks of treatment is 96% (363/380) and 96% (324/339), respectively. The positive predictive value for 48 and 72 weeks of treatment is 35% (20/57) and 57% (57/100), respectively.

Discontinuation of treatment

Discontinuation of treatment is recommended if at least a 2 log10 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 modifications

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 Warnings and Precautions and 2.6 Undesirable Effects).

Dose modification for Pegasys in adult patients

Hematological: for adults, dose reduction is recommended if the 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/mm^3. Cessation of therapy is recommended when platelet count decreases to levels below 25,000/mm^3.

Dose modification for ribavirin in Chronic Hepatitis C when administered in combination therapy

For management of treatment-emergent anemia in adults, 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 judgement. However, it is not recommended that ribavirin be increased to the original dose (1000 mg or 1200 mg).

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

2.2.1 Special Dosage Instructions

Pediatric use

Currently available data are described in section 2.5.4 Use in Special Populations, Pediatric Use.

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 Pharmacokinetics 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 adult patients, the dose should be reduced initially to 135 mcg in the presence of progressive 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 2.4 Warnings and 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. 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 2.4 Warnings and Precautions).

2.3 Contraindications

- Hypersensitivity to alpha interferons, to *E. coli*-derived products, to polyethyleneglycol or to any component of the product.
- Autoimmune hepatitis.
- Decompensated cirrhosis.
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months.
- Initiation of Pegasys is contraindicated in HIV-HCV patients with cirrhosis and Child-Pugh score ≥6, except if only due to indirect hyperbilirubinemia caused by drugs such as atazanavir and indinavir.
- Combination with telbivudine.
- Neonates and infants up to 3 years of age.
- Due to the use of ribavirin, pregnant women must not be exposed to Pegasys/ribavirin combination therapy (please refer to section *2.5.1 Pregnancy)*.

Please refer also to the approved ribavirin prescribing information when Pegasys is used in combination with ribavirin.

2.4 Warnings and Precautions

2.4.1 General

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 administered under the guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of further therapy.

Please refer to the approved ribavirin prescribing information regarding other laboratory entrance criteria.

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 Undesirable Effects). In clinical studies, progressive decreases, after 4 to 8 weeks of treatment were infrequent. Dose reduction is recommended when ANC decreases to levels below 750 cells/mm^3 (see section 2.2 Dosage and Administration). 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 Undesirable Effects). 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 Dosage and Administration).

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 2.6.1.1 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 hematogical adverse events. Physician considering treatment in these patients should carefully weigh the risks versus the benefits of retreatment.

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 Dosage and Administration). As with other interferons, caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agent.

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 Interactions with other Medicinal Products and other Forms of Interaction).

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.

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.

Autoimmune Disorder

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. 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.

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.

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 therapy.

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 alfpha 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.

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 Pegasys. All patients should have a baseline eye examination. Patients with pre-existing ophthalmologic disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during alpha interferon treatment. Any patient complaining of decreased or loss of vision must have a prompt and complete eye examination. Pegasys or Pegasys/ribavirin should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Cardiovascular

Because cardiac disease may be worsened by ribavirin-induced anemia, HCV patients with a history of significant or unstable cardiac disease in the previous six months should not use ribavirin. Cardiovascular events such as hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with 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 (see section 2.2 Dosage and Administration and refer also to the approved ribavirin prescribing information).

Hypersensitivity

Serious, acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If such a reaction develops during treatment 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.

Hepatic Function

In patients who develop evidence of hepatic decompensation during treatment, Pegasys or Pegasys/ribavirin should be discontinued.

HCV: As with other alpha interferons, increases in ALT levels above baseline have been observed in patients treated 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 bilirubin, therapy should be discontinued (see section 2.2 Dosage and Administration).

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.

HIV-HCV Co-infection

Co-infected patients with advanced cirrhosis receiving concomitant HAART may be at an increased risk of hepatic decompensation and possibly death when treated with alpha interferons, including Pegasys, with or without ribavirin. 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 ≥7). 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.

2.4.2 Ability to Drive and Use Machines

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

2.4.3 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 cells/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.

Please refer also to the approved ribavirin prescribing information when Pegasys is used in combination with ribavirin.

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 and/or ribavirin are excreted in human breast 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 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 Contraindications).

2.5.5 Geriatric Use

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

2.5.5 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 end stage renal disease, a starting dose of Pegasys 135 mcg once weekly should be used (see section 3.2.5 Pharmacokinetics 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 (see section 2.2.1 Special Dosage Instructions, Dose modification for Pegasys, General). Please refer to the approved ribavirin prescribing information for information regarding the use of ribavirin in patients with renal impairment.

2.5.6 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 bleeding esophageal varices) (see section 2.3 Contraindications).

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

Modified Assessment

Assessment	Degree of abnormality	Score
Encephalopathy	None	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)

2.6 Undesirable Effects

The adverse reactions observed with other alpha interferons, alone or in combination with ribavirin, may be expected with Pegasys or Pegasys/ribavirin combination therapy, respectively.

2.6.1 Clinical Trials

The frequency and severity of the most commonly reported adverse reactions are similar in patients treated with Pegasys or Pegasys/ribavirin and alpha interferon or alpha interferon with ribavirin, respectively.

The most frequently reported adverse reactions with Pegasys and Pegasys/ribavirin were mostly mild to moderate in severity and were manageable without the need for modification of dosage or discontinuation of therapy.

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 (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 hematologic 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% (see section 2.4.1 Warnings and Precautions).

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. CD4+ cell count indices returned to baseline values during the follow-up period of the study. Pegasys containing treatment had no apparent negative impact on the control of HIV viremia during therapy or follow-up.

Chronic Hepatitis B

In clinical trials of 48 week treatment and 24 weeks follow-up, the safety profile for Pegasys in CHB was similar to that seen in CHC, although the frequency of reported adverse events was notably less in CHB (see Table 3). 88% of Pegasys-treated patients experienced adverse events, 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.

Table 3 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 3 Adverse Reactions (≥ 10% Incidence in Any Treatment Group) in Adult Patients

	HBV	HCV				HIV-HCV	HCV non-responder to prior peginterferon alfa-2b therapy
Body System	**PEG 180 mcg*** **48 wk (WV16240 + WV16241)**	**PEG 180 mcg** **48 wk (NV15801 + monotherapy program)**	**PEG 180 mcg + 800 mg ribavirin** **24 wk (NV15942)**	**PEG 180 mcg + 1000 mg or 1200 mg ribavirin** **48 wk (NV15801 + NV15942)**	**IFN alfa-2b + 1000 mg or 1200 mg ribavirin** **48 wk (NV15801)**	**PEG 180 mcg + 800 mg ribavirin** **48 wk (NV15961)**	**PEG 180 mcg + 1000 mg or 1200 mg ribavirin** **72 wk (MV17150)**
	N=448	**N=827**	**N=207**	**N=887**	**N=443**	**N=288**	**N=156**
	%	**%**	**%**	**%**	**%**	**%**	**%**
Metabolism and nutrition disorders							
Anorexia	13	16	20	27	26	23	15
Weight decrease	4	5	2	7	10	16	9
Psychiatric disorders							
Insomnia	6	20	30	32	37	19	29
Depression	4	18	17	21	28	22	16
Irritability	3	17	28	24	27	15	17
Concentration impairment	2	9	8	10	13	2	5
Anxiety	3	6	8	8	12	8	6
Nervous system disorders							
Headache	23	52	48	47	49	35	32
Dizziness (excluding vertigo)	6	15	13	15	14	7	10
Respiratory, thoracic and mediastinal disorders							
Dyspnea	1	5	11	13	14	7	11
Cough	2	4	8	13	7	3	17

	HBV	HCV				HIV-HCV	HCV non-responder to prior peginterferon alfa-2b therapy
Body System	**PEG 180 mcg* 48 wk (WV16240 + WV16241)**	**PEG 180 mcg 48 wk (NV15801 + monotherapy program)**	**PEG 180 mcg + 800 mg ribavirin 24 wk (NV15942)**	**PEG 180 mcg + 1000 mg or 1200 mg ribavirin 48 wk (NV15801 + NV15942)**	**IFN alfa-2b + 1000 mg or 1200 mg ribavirin 48 wk (NV15801)**	**PEG 180 mcg + 800 mg ribavirin 48 wk (NV15961)**	**PEG 180 mcg + 1000 mg or 1200 mg ribavirin 72 wk (MV17150)**
Gastrointestinal disorders							
Nausea	6	24	29	28	28	24	24
Diarrhea	6	16	15	14	10	16	13
Abdominal pain	4	15	9	10	9	7	9
Skin and subcutaneous tissue disorders							
Alopecia	17	23	25	24	33	10	18
Pruritus	6	13	25	21	18	5	22
Dermatitis	<1	9	15	16	13	1	1
Dry skin	1	5	13	12	13	4	17
Musculoskeletal, connective tissue and bone disorders							
Myalgia	25	37	42	38	49	32	22
Arthralgia	10	26	20	22	23	16	15
General disorders and administration site conditions							
Fatigue	21	49	45	49	53	40	36
Pyrexia	52	35	37	39	54	41	20
Rigors	6	30	30	25	34	16	12
Injection site reaction	7	22	28	21	16	10	12
Pain	1	11	9	10	9	6	6
Asthenia	11	7	18	15	16	26	30

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

Adverse reaction reported in ≥1% but <10% on Pegasys/ribavirin combination or Pegasys monotherapy in HBV, HCV and HIV-HCV adult 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 disorder*s: flushing
Respiratory, thoracic and mediastinal disorders: sore throat, rhinitis, nasopharyngitis, sinus congestion, dyspnea exertional, epistaxis
Gastrointestinal disorders: vomiting, dyspepsia, gastritis, 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.

Rarely, alpha interferon including Pegasys, used in combination with ribavirin, may be associated with pancytopenia, and very rarely aplastic anemia has been reported.

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 section 2.4 Warnings and Precautions and 2.2.1 Special Dosage Instructions). Although haematological 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 HCV patients, including those with cirrhosis, required dose modification for anemia. Approximately 10% of HCV patients on 48 weeks Pegasys/ribavirin 1000/1200 mg combination therapy required dose modification for anemia. Anemia (haemoglobin <10 g/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 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 HCV 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 cells/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 platelet 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 Warnings and Precautions). 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.

2.6.2 Post Marketing Experience

During the post-marketing period, erythema multiforme, Steven 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, serious 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.

Respiratory, thoracic and mediastinal disorders: Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). 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. 1260 mcg/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 Medicinal 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 95 mg; range 30 mg to 150 mg), treatment with Pegasys 180 mcg s.c. 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 anti-retroviral therapy 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 cannot 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.

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 2.4.1).

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

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.

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

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.

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 180 mcg Pegasys and stays maximal throughout the one-week dosing interval. The magnitude and duration of 2',5'-oligoadenylate synthetase activity induced by Pegasys 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

Chronic 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 4. HBV DNA was measured by the COBAS AMPLICOR HBV MONITOR Assay (limit of detection 200 copies/mL).

Table 4. Serological, Virological and Biochemical Responses in Adult Patients with Chronic Hepatitis B

	HBeAg positive Study WV16240			**HBeAg negative / anti-HBe positive Study WV16241**		
	Pegasys 180 mcg and **Placebo** (N=271)	**Pegasys** 180 mcg and **Lamivudine** 100 mg (N=271)	**Lamivudine** 100 mg (N=272)	**Pegasys** 180 mcg and **Placebo** (N=177)	**Pegasys** 180 mcg and **Lamivudine** 100 mg (N=179)	**Lamivudine** 100 mg (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 $<2 \times 10^4$ 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

Chronic Hepatitis C

Clinical studies have demonstrated that Pegasys alone or in combination with ribavirin is effective in the treatment of patients with CHC, including cirrhotic patients with compensated liver disease, as well as, in patients with HIV-HCV co-infection.

Confirmatory clinical trials in naïve patients

All clinical trials recruited interferon-naïve patients with CHC confirmed by detectable levels of serum HCV RNA, elevated levels of ALT 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%).

For treatment regimens, duration of therapy and study outcome see Tables 5 and 6. 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 5. Virological Response in Chronic Hepatitis C

	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	**Inter-feron alfa-2a** 6 MIU/ 3 MIU and 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 and **Ribavirin** 1000/1200 mg (N=436) 48 weeks	**Pegasys** 180 mcg and **Ribavirin** 1000/1200 mg (N=453) 48 weeks	**Interferon alfa-2b** 3 MIU and **Ribavirin** 1000/1200 mg (N=444) 48 weeks
Response at End of Treatment	55 - 69%	22 - 28%	44%	14%	68%	69%	52%
Overall Sustained Response	28 - 39%	11 - 19%	30%*	8%*	63%	54%**	45%**

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

The virological responses of patients treated with Pegasys and ribavirin combination based on genotype and viral load are summarised in Table 6. The results of study NV15942 provide the rationale for recommending treatment regimen 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 6 Sustained Virological Response in Chronic Hepatitis C based on Genotype and Viral Load after Pegasys Combination Therapy with ribavirin

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

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

Superior efficacy of Pegasys compared to interferon alfa-2a was demonstrated also in terms of histological response, including patients with cirrhosis, as well as, in HIV-HCV co-infected patients.

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 study NV15942 (see Table 7).

Table 7 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		
	Pegasys 180 mcg & **Ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 mcg & **Ribavirin** 1000/1200 mg 48 weeks
Genotype 1 RVR	90% (28/31)	92% (47/51)

Low viral load	93% (25/27)	96% (26/27)
High viral load	75% (3/4)	88% (21/24)
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)
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

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response by week 4 in study NV17317 (see Table 8).

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 was not equivalent to treatment for 24 weeks (see Table 8). Treatment for 16 weeks resulted in lower sustained viral response (65%) than treatment for 24 weeks (76%). However a retrospective analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline showed that the sustained viral response achieved with 16 weeks of treatment was comparable to that achieved with 24 weeks of treatment (89% and 94%, respectively) (see Table 8).

Table 8 Sustained Virological Response Based on Rapid Viral Response at week 4 for Genotype 2 and 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
Genotype 2 or 3	65% (443/679)	76% (478/630)
Genotype 2 or 3 RVR	82% (378/461)	90% (370/410)
Low viral load	89% (147/166)	94% (141/150)
High viral load	78% (231/295)	88% (229/260)
Genotype 2 or 3 non RVR	30% (65/218)	49% (108/220)
Low viral load	44% (22/50)	50% (25/50)
High viral load	26% (43/168)	49% (83/170)

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

Chronic Hepatitis C prior treatment non-responder patients

In Study MV17150, patients who were previous non-responders to pegylated interferon alfa-2b plus ribavirin therapy 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; or Pegasys 180 mcg/week for 48 weeks. All patients received ribavirin (1,000 or 1,200 mg/day) in combination with Pegasys. All treatments had 24 week treatment-free follow up. The sustained virological responses from a pooled analysis comparing duration of therapy or Pegasys induction dosing are summarized Table 9.

Table 9 Sustained Virological Response in Previous PEG-IFN alfa 2b/Ribavirin Non-responders: Pooled Treatment Comparisons

MV17150				
	72 week Groups N = 473	48 week Groups N = 469	360 mcg Groups N = 473	180 mcg Groups N = 469
SVR	16%*	8%*	13%	10%

* 95% confidence interval (CI) of 1.40 to 3.52 and a p-value of 0.00061

The sustained virological response rate after 72 weeks treatment was superior to that after 48 weeks.

Differences in sustained virological response based on treatment duration and demographics found in study MV17150 are displayed in Table 10.

Table 10 Sustained Virological Response after treatment with Pegasys and Ribavirin Combination Therapy in Non-responders to Previous Treatment with Peginterferon alfa-2b/ribavirin

	Peginterferon alfa-2b/ribavirin NRs Re-treated for 48 weeks % (N)	**Peginterferon alfa-2b/ribavirin NRs Re-treated for 72 weeks % (N)**
Overall NR	8% (38/469)	16% (74/473)
Genotype 1/4	7% (33/450)	15% (68/457)
Genotype 2/3	25% (4/16)	33% (5/15)
Genotype		
1	7% (31/426)	14% (60/430)
2	0 (0/4)	33% (1/3)
3	33% (4/12)	33% (4/12)
4	8% (2/24)	30% (8/27)
Baseline Viral Load		
HVL (greater than 800,000 IU/mL)	7% (25/363)	12% (46/372)
LVL (less than or equal to 800,000 IU/mL)	13% (11/84)	31% (27/86)

In the HALT-C study, patients with chronic hepatitis C and advanced fibrosis or cirrhosis who had not responded to previous treatment with interferon alfa or pegylated interferon alfa monotherapy or combination ribavirin therapy 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. Sustained virological response varied depending upon the previous treatment regimen. Treatment outcome was poorest among patients who were non-responders to pegylated interferon in combination with ribavirin, identifying the most difficult to treat subpopulation of non-responder patients, and comparable with the sustained virological response rate observed in the 48 week treatment arms of MV17150. Despite higher sustained virological response in non-responders to interferon or pegylated interferon monotherapy, efficacy in these less difficult to treat non-responders remains substantially lower than what is achievable in treatment-naïve patients (see Table 11).

Table 11 SVR rates by Treatment Duration and Non-responder Population

Treatment Duration	**Interferon**	**Pegylated Interferon**	**Interferon plus Ribavirin**	**Pegylated interferon plus Ribavirin**	
48 weeks	27% (70/255)*	34% (13/38)*	13% (90/692)*	11% (7/61)*	8% (38/469)**
72 weeks	-	-	-	-	16% (74/473)**

* data from HALT-C
** data from MV17150

Chronic Hepatitis C prior treatment relapser patients

In a study in predominantly genotype 1 chronic hepatitis C patients who had relapsed after 48 weeks of combination treatment with pegylated interferon alfa-2 plus ribavirin, patients were treated for 72 weeks with the combination of either Pegasys 180 mcg/week plus weight-based ribavirin daily or consensus interferon (9 mcg) daily plus weight-based ribavirin daily. The sustained virological response was 42% for patients treated with Pegasys and ribavirin combination therapy for 72 weeks.

In an open-label, study in genotype 2 and 3 chronic hepatitis C patients who relapsed after treatment for 24 weeks with Pegasys and ribavirin combination therapy, patients were treated with Pegasys 180 mcg/week and ribavirin 1000 or 1200 mg (by weight) daily combination therapy for 48 weeks and then followed treatment-free for 24 weeks. The sustained virological response was 64%.

HIV-HCV Co-Infection

In study NR15961, 860 HIV-HCV co-infected patients were randomized and treated with Pegasys 180 mcg/week and placebo, Pegasys 180 mcg/week and ribavirin 800 mg/day or interferon alfa-2a 3 MIU three times weekly and ribavirin 800 mg/day for 48 weeks followed by a 24 week treatment-free follow-up. The sustained virologic responses for the three treatment groups are summarized for all patients and by genotype in Table 12.

Table 12 Sustained Virologic Response in HIV-HCV Co-infected Patients

	PEGASYS 180 mcg + Placebo 48 weeks	**PEGASYS** 180 mcg + ribavirin 800 mg 48 weeks	**Interferon alfa-2a** 3MIU + ribavirin 800 mg 48 weeks
All patients	20% (58/286)*****	40% (116/289)*****	12% (33/285)*****

Genotype 1	14% (24/175)	29% (51/176)	7% (12/171)
Genotype 2/3	36% (32/90)	62% (59/95)	20% (18/89)

* Pegasys 180 mcg ribavirin 800 mg *vs*. Interferon alfa-2a 3MIU ribavirin 800mg: 95% CI for difference: 22% to 35%, p-value (stratified Cochran-Mantel-Haenszel test) = <0.0001
* Pegasys 180 mcg ribavirin 800 mg *vs*. Pegasys 180 mcg: 95% CI for difference: 13% to 27%, p-value (stratified Cochran-Mantel-Haenszel test) = <0.0001

3.2 Pharmacokinetic Properties

The pharmacokinetics of Pegasys were studied in healthy volunteers and hepatitis C virus-infected patients (see Table 13). 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 180 mcg. 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

Pegasys is found predominately in the bloodstream and extracellular fluid as seen by the volume of distribution at steady-state (V_{ss}) of 6 to 14 liters after intravenous dosing in humans. 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 in healthy subjects is approximately 60 hours compared with values of 3 to 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 determined after subcutaneous administration may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Pegasys.

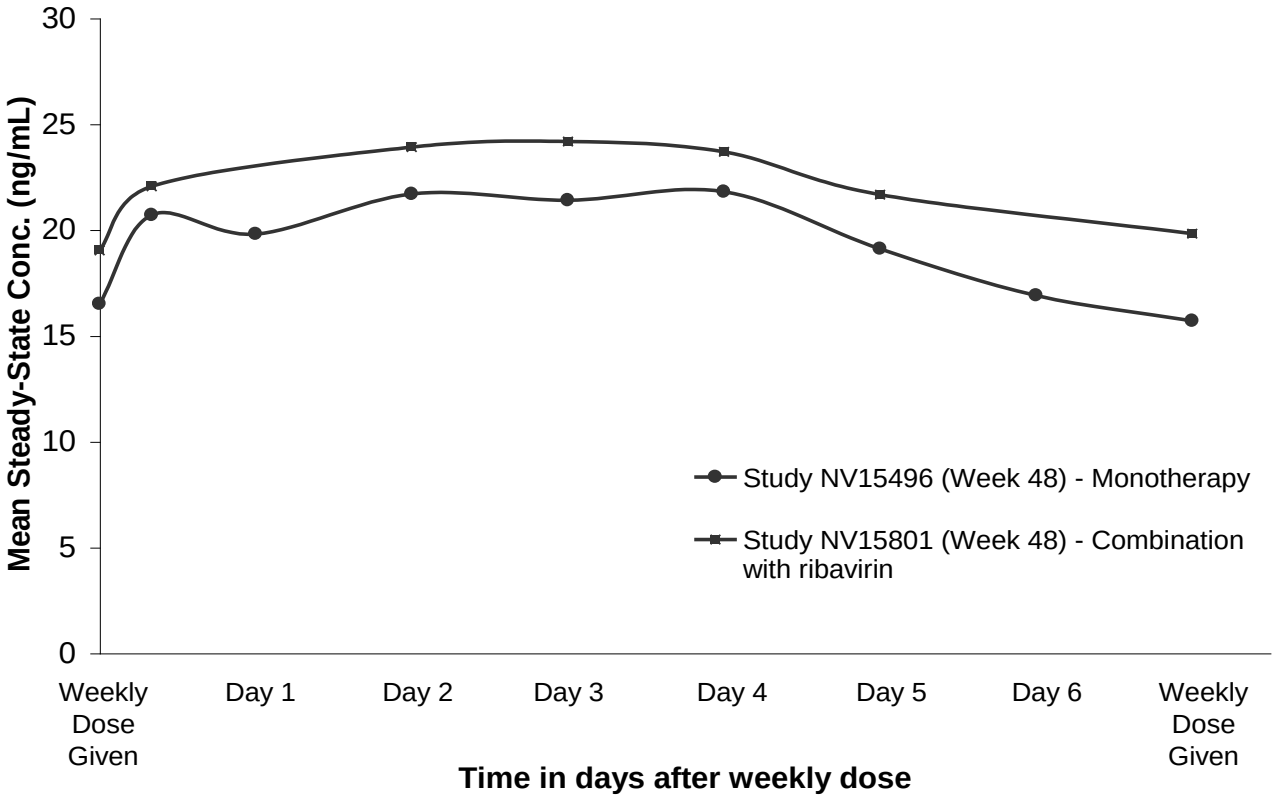
Dose-proportional increases in AUC and C_{max} are seen in healthy subjects and patients with chronic hepatitis C after once-weekly doses of Pegasys. The pharmacokinetic parameters of Pegasys are given in Table 13 for healthy subjects receiving a single subcutaneous injection of 180 mcg of Pegasys and for patients with chronic hepatitis C receiving 48 weeks of 180 mcg of Pegasys once-weekly.

Table 13 Pharmacokinetic Parameters of Pegasys after Single and Multiple Dose of 180 mcg

	Healthy Subjects 180 mcg sc (N=50)	**CHC Patients in NV15496 180 mcg 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) (see 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 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 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, 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 2.2 Dosage and Administration).

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 Nonclinical 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.

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 Carcinogecity

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 Storage

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

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

4.2 Special 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.

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, pre-filled pens 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, pre-filled pens and needles should be supplied to the patients.

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

4.3 Packs

Pegasys Pre-Filled Syringe 135 mcg	1, 4
Pegasys Pre-Filled Syringe 180 mcg	1, 4

Medicine: keep out of reach of children

MYPegasys20210507CDS20.0

Date of revision: May 2021

Roche

Pegasys Pre-Filled Syringes
Made in Switzerland by
F. Hoffmann-La Roche Ltd, Basel
manufacturing site Kaiseraugst.