NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Pegasys (peginterferon alfa-2a) 180mcg/0.5mLsolution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Pegasys 180 micrograms solution for injection in pre-filled syringe. Each syringe of 0.5mL solution contains 180 micrograms of peginterferon alfa-2a.

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

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
Solution for injection.

The solution is clear and colourless to light yellow, practically free of particles.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Chronic hepatitis B (CHB)
Pegasys is indicated for the treatment of both HBeAg-positive and HBeAg-negative CHB in non-cirrhotic and cirrhotic patients with compensated liver disease and evidence of viral replication and liver inflammation.

Chronic hepatitis C (CHC)
Pegasys alone or in combination with ribavirin is indicated for the treatment of CHC in non-cirrhotic and cirrhotic patients with compensated liver disease.

4.2 DOSE AND METHOD OF ADMINISTRATION
Before beginning Pegasys, standard haematological and biochemical laboratory tests are recommended for all patients (see section 4.4 Special warnings and precautions for use).

Dose
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: treatment-naïve, prior treatment non-responder and relapser patients
The recommended dosage of Pegasys, alone or in combination with ribavirin, is 180 mcg once a week by subcutaneous administration in the abdomen or thigh.

Ribavirin should be administered in divided doses (morning and evening) with food.

The recommended duration of Pegasys monotherapy is 48 weeks.

The duration of combination therapy and the daily dose of ribavirin given in combination with Pegasys should be individualised based on the patient's viral genotype (see Table 1).

Table 1 Dosing Recommendations

Genotype	Pegasys dose	Ribavirin dose	Duration of treatment: naïve patients	Duration of treatment: prior treatment non-responder and relapser patients
Genotype 1, 4*	180 mcg	< 75 kg = 1000 mg 5 tablets (2 morning, 3 evening)	48 weeks	72 weeks
		≥ 75 kg = 1200 mg 6 tablets (3 morning, 3 evening)	48 weeks	72 weeks
Genotype 2, 3	180 mcg	800 mg 4 tablets (2 morning, 2 evening)	24 weeks	48 weeks

** 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.*

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 HCV Patients

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 retrospectively, 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 is 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 modification for Pegasys

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

Haematological

Dose reduction is recommended if the absolute neutrophil count (ANC) is less than 0.75 x 10^9/L. For patients with ANC values below 0.5 x 10^9/L, treatment should be suspended until ANC values return to more than 1 x 10^9/L. 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 x 10^9/L. Cessation of therapy is recommended when platelet count decreases to levels below 25 x 10^9/L.

Liver impairment

Fluctuations in abnormalities of liver function tests are common in patients with chronic hepatitis. However, as with other alfa 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 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 4.4 Special warnings and precautions for use).

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 4.4 Special warnings and precautions for use).

Dose modification for ribavirin when administered in combination therapy

For management of treatment-emergent anaemia, 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 haemoglobin to < 100 g/L and ≥ 85 g/L or
- A patient with stable cardiovascular disease experiences a fall in haemoglobin by ≥ 20 g/L 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 haemoglobin to < 85 g/L.
- If a patient with stable cardiovascular disease maintains a haemoglobin value < 120 g/L 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.

Special populations

Paediatric 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 4.3 Contraindications).

Use in the elderly

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

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 5.2 Pharmacokinetic properties, 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. Please refer to the approved ribavirin prescribing information for information regarding the use of ribavirin in patients with renal impairment.

No data is available on the use of Pegasys in paediatric patients with renal impairment.

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 oesophageal varices) (see section 4.3 Contraindications).

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

Modified Assessment

Assessment	Degree of abnormality	Score
Encephalopathy	None Grade 1 - 2 Grade 3 - 4*	1 2 3
Ascites	Absent Slight Moderate	1 2 3
S-Bilirubin (mg/dL) SI unit = mcmol/L	< 2 2 - 3 > 3 < 34 34 - 51 > 51	1 2 3 1 2 3
S-Albumin (g/L)	> 35 35 - 28 < 28	1 2 3
INR	< 1.7 1.7 - 2.3 > 2.3	1 2 3

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

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
Pegasys is contraindicated in patients with known hypersensitivity to alfa interferons, to E. coli-derived products, to polyethyleneglycol or to any component of the product.

- Pegasys is contraindicated in patients with autoimmune hepatitis.
- Pegasys is contraindicated in patients with decompensated cirrhosis.
- 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 medicines such as atazanavir and indinavir.
- Pegasys is contraindicated for use in neonates and infants up to 3 years of age.
- Pegasys/ribavirin combination therapy must not be used in women who are pregnant.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 in the patient medical

record. Substitution by any other biological medicinal product requires the consent of the prescribing physician.

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.

The use of Pegasys and ribavirin combination therapy in CHC patients who discontinued hepatitis C therapy for haematological adverse events has not been adequately studied. Physicians considering treatment in these patients should carefully weigh the risks versus the benefits of re-treatment.

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 4.8 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 0.75 x 10^9/L (see section 4.2 Dose and method of administration). For patients with ANC values below 0.5 x 10^9/L, treatment should be suspended until ANC values return to more than 1 x 10^9/L. 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 pre-treatment (baseline) levels during the post-treatment observation period (see section 4.8 Undesirable effects). Dose reduction is recommended when platelet count decreases to levels below 50 x 10^9/L and cessation of therapy is recommended when platelet count decreases to levels below 25 x 10^9/L (see section 4.2 Dose and method of administration).

Anaemia (haemoglobin $\leq$100 g/L) 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 Undesirable Effects, Laboratory test values–haemoglobin and haematocrit). The maximum drop in haemoglobin occurred within 4 weeks of initiation of ribavirin therapy. Full blood counts should be obtained pre-treatment, 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 4.2 Dose and method of administration). Please refer also to the approved ribavirin prescribing information.

It is advised that full blood counts (FBC) be obtained pre-treatment and monitored routinely during therapy. Pegasys monotherapy or Pegasys/ribavirin combination therapy should be used with caution in patients with baseline neutrophil counts < 1.5 x 10^9/L, with baseline platelet count < 90 x 10^9/L or baseline haemoglobin < 120 g/L (see section 4.2 Dose and method of administration). As with other interferons, caution should be exercised when administering Pegasys in combination with other potentially myelosuppressive agents.

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 4.5 Interactions

with other medicines and other forms of interactions). When used in combination with ribavirin, please refer to the ribavirin prescribing information.

Organ transplant recipients
The safety and efficacy of Pegasys and ribavirin combination therapy have not been established in patients with liver and other transplantations. As with other alfa interferons, liver and renal graft rejections have been reported with 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 alfa interferons including Pegasys. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

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

Use of alfa 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.

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. Hyperglycaemia, hypoglycaemia and diabetes mellitus have been observed in patients treated with alfa 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.

Neuropsychiatric
Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including Pegasys or Pegasys/ribavirin. Depression, suicidal ideation, and suicidal attempt may occur in patients with and without previous psychiatric illness. 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 therapy, and patients should report any sign or symptom of depression immediately. In severe cases therapy should be stopped and psychiatric intervention sought (see section 4.8 Undesirable effects).
Exercise caution and monitor for evidence of depression when administering Pegasys to paediatric patients with a prior history of or concurrent psychiatric disorders.

Ophthalmologic
As with other interferons, retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy, and retinal artery or vein obstruction, which may result in loss of vision, have been reported 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 alfa 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 anaemia, 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 4.2 Dose and method of administration).

Hypersensitivity
Serious, acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alfa 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.

Growth and Development (paediatric patients)
During the course of Pegasys plus ribavirin therapy lasting up to 48 weeks in patients aged 5 to 17 years, weight loss and growth inhibition were common.

At 2 years post-treatment, 16% of paediatric patients were more than 15 percentiles below their baseline weight curve and 11% were more than 15 percentiles below their baseline height curve.

At 5 to 6 years post-treatment, paediatric patients who were more than 15 percentiles below their baseline at 2 years post-treatment, either returned to baseline comparable height percentiles or a non-treatment related causative factor has been identified. The long term follow up data suggests that Pegasys treatment is unlikely to be associated with a sustained growth inhibition in children. The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials on a case by case basis.

It is important to consider that the combination therapy induced a growth inhibition during treatment.

This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression, as well as prognostic factors of response (HCV genotype and viral load).

Pulmonary
As with other alfa interferons, pulmonary symptoms, including dyspnoea, 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 impairment
In patients who develop evidence of hepatic decompensation during treatment, Pegasys or Pegasys/ribavirin should be discontinued.

HCV: As with other alfa 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 bilirubin, therapy should be discontinued (see section 4.2 Dose and method of administration).

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

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 5.2 Pharmacokinetic properties).

Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of Pegasys during the course of therapy should be made in the event of adverse reactions. (see section 4.2 Dose and method of administration, Dose modification). Please refer to the approved ribavirin prescribing information for information regarding the use of ribavirin in patients with renal impairment.

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 alfa 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 $\geq$ 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.

Laboratory tests
Before beginning Pegasys monotherapy or Pegasys/ribavirin combination therapy, standard haematological and biochemical laboratory tests are recommended for all patients. After initiation of therapy, haematological 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:

- Haemoglobin ≥ 120 g/L (females); ≥ 130 g/L (males)
- Platelet count 90 x 10^9/L
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- TSH and T_4 within normal limits or adequately controlled thyroid function
- HIV-HCV co-infection: CD4+ ≥ 200/mcL or CD4+ ≥ 100/mcL to < 200/mcL and HIV-1 RNA < 5000 copies/mL using Amplicor HIV-1 Monitor Test, v 1.5

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

Any potential for interactions may persist for up to 2 months (5 half-lives for ribavirin) after cessation of ribavirin therapy due to its long half-life.

Treatment with Pegasys 180 mcg once a week 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 alfa interferons. Alfa interferons have been shown to affect the oxidative metabolism of some medicines 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 therapies 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 subcutaneously 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.

Nucleoside analogues
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.

Didanosine
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 hyperlactataemia/lactic acidosis have been reported with use of ribavirin.

Telbivudine
A clinical trial investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa-2a, 180 mcg once a week 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 haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicines should be stopped (see section 4.4 Special warnings and precautions for use)

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy – Category B3
Pegasys should not be used in pregnant women. Pegasys has not been studied for its effect on fertility. As with other alfa interferons, prolongation of the menstrual cycle accompanied by both a decrease and a delay in the peak of 17β-oestradiol 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.

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 alfa

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.

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

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

Breast-feeding
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 should be made either to discontinue breast-feeding or discontinue treatment, based on the importance of the therapy to the mother.

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

Teratogenicity
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.

4.7 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.

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

Experience from clinical trials
The frequency and severity of the most commonly reported adverse reactions are similar in patients treated with Pegasys or Pegasys/ribavirin and alfa interferon or alfa 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 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.

Chronic hepatitis C

Treatment naïve patients

In clinical trials, the incidence of withdrawal from treatment for all naïve 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%).

Prior treatment non-responder patients

In study MV17150 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 with the 48 week arms (6% and 6%). Patients who withdrew from previous therapy due to haematological toxicity were excluded from enrolling in this trial.

In the HALT C study, patients with advanced fibrosis or cirrhosis (Ishak score of 3 - 6) were enrolled with baseline platelet counts as low as 50 x 10^9/L and treated for 48 weeks (see section 5.1 Pharmacodynamic properties, Clinical trials). 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: haemoglobin < 100 g/L, 26.3%; absolute neutrophil counts (ANC) < 0.75 x 10^9/L, 30%; and platelet < 50 x 10^9/L, 13% (see section 4.4Special warnings and precautions for use).

HIV-HCV co-infection

In study NR15961, 180 mcg Pegasys with and without 800 mg ribavirin in HIV-HCV co-infected patients, the clinical adverse events reported on Pegasys, alone or in combination with ribavirin, were similar to those observed in HCV mono-infected patients. Limited safety data (n = 51) is available in co-infected patients with CD4+ cell counts < 200/mcL. 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, due to blood and lymphatic system disorder adverse event. 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.

Study NV18209 compared 48 weeks of treatment with either Pegasys 180 mcg plus ribavirin 1000 or 1200 mg or Pegasys 180 mcg plus ribavirin 800 mg in interferon-naïve patients with HIV-HCV co-infected patients (HCV genotype 1 virus). 275 patients received the ribavirin 1000/1200 mg regime and 135 patients received the 800 mg regime. 80% of patients were male, median age 46 years, 64% Caucasian and 30% non-Hispanic African Americans. Over half of the patients in both treatment groups prematurely withdrew from either treatment and from either treatment group for safety (12 – 13%) or non-safety reasons (40 – 45%). The primary non-safety reason for premature withdrawal was insufficient therapeutic response (25 – 26%). The incidence of withdrawal for safety reasons was 12% (abnormal laboratory tests 4%, adverse events 8 – 9%). The incidence of adverse reactions of ≥ 10% of patients in study NV18209 were similar to those within Table 3 for HIV-HCV co-infected patients, with no increased frequency for Pegasys plus ribavirin 1000/1200 mg compared with Pegasys plus ribavirin 800 mg except for anaemia (see Laboratory test values below).

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)

	HBV (treatment naïve)	**HCV (treatment naïve)**				**HIV-HCV (treatment naïve)**	**HCV non responder to prior peginterferon alfa-2b treatment**
Body System	**Pegasys 180 mcg* 48 wk (WV16240 + WV16241)**	**Pegasys 180 mcg 48 wk (NV15801 + monotherapy program)**	**Pegasys 180 mcg + 800 mg ribavirin 24 wk (NV15942)**	**Pegasys 180 mcg + 1000 mg or 1200 mg ribavirin 48 wk (NV15801 + NV15942)**	**IFN alfa-2b + 1000 mg or 1200 mg ribavirin 48 wk (NV15801)**	**Pegasys 180 mcg + 800 mg ribavirin 48 wk (NV15961)**	**Pegasys 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							
Dyspnoea	*1*	5	11	13	14	7	11
Cough	2	4	8	13	7	3	17
Gastrointestinal disorders							
Nausea	6	24	29	28	28	24	24
Diarrhoea	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

	HBV (treatment naïve)	HCV (treatment naïve)				HIV-HCV (treatment naïve)	HCV non responder to prior peginterferon alfa-2b treatment
Body System	**Pegasys 180 mcg* 48 wk (WV16240 + WV16241)**	**Pegasys 180 mcg 48 wk (NV15801 + monotherapy program)**	**Pegasys 180 mcg + 800 mg ribavirin 24 wk (NV15942)**	**Pegasys 180 mcg + 1000 mg or 1200 mg ribavirin 48 wk (NV15801 + NV15942)**	**IFN alfa-2b + 1000 mg or 1200 mg ribavirin 48 wk (NV15801)**	**Pegasys 180 mcg + 800 mg ribavirin 48 wk (NV15961)**	**Pegasys 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
	%	%	%	%	%	%	%
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 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, anaemia, thrombocytopenia

Endocrine disorders: hypothyroidism, hyperthyroidism

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

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

Ear and labyrinth disorders: vertigo, earache

Cardiac disorders: palpitations, oedema peripheral, tachycardia

Vascular disorders: flushing

Respiratory, thoracic and mediastinal disorders: sore throat, rhinitis, nasopharyngitis, sinus congestion, dyspnoea 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: hyperlactacidaemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

As with other alfa 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 and cerebral haemorrhage, TTP, psychotic disorder and hallucination.

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

Haematology
As with other interferons, treatment with either Pegasys or Pegasys/ribavirin was associated with decreases in haematological values, which generally improved with dosage modification and returned to pre-treatment levels within 4 to 8 weeks upon cessation of therapy (see sections 4.4 Special warnings and precautions for use and 4.2 Dose and method of administration). Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment.

Haemoglobin and haematocrit
Although treatment with Pegasys monotherapy was associated with small gradual decreases in haemoglobin and haematocrit, less than 1% of all HCV patients, including those with cirrhosis, required dose modification for anaemia. Approximately 10% of HCV patients on

48 weeks Pegasys/ribavirin 1000/1200 mg combination therapy required dose modification for anaemia. Anaemia (haemoglobin < 100 g/L) was reported in 7%, 14% and 28% of HIV-HCV co-infected patients treated with Pegasys monotherapy or in combination with ribavirin 800 mg and 1000/1200 mg respectively in studies NR15961 and NV18209.

In study NV18209, patients with anaemia were clinically managed with the use of growth factors and transfusions 26% and 37% of patients in the Pegasys plus ribavirin 800 mg group and in the Pegasys plus ribavirin 1000/1200 mg groups respectively, and with dose modification of either treatment in 13% and 21% of patients, 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 0.5 x 10^9/L 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 0.5 x 10^9/L.

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 x 10^9/L, mostly in patients with cirrhosis and who entered the study with baseline platelet counts as low as 75 x 10^9/L. In clinical trials for hepatitis B, 14% of patients had decreases in platelet counts to below 50 x 10^9/L, 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 x 10^9/L.

Hepatic function

Transient and potentially significant increases in serum ALT are not uncommon in hepatitis B. While on therapy, elevations of ALT are indicative of immune mediated destruction of infected hepatocytes and may precede HBeAg seroconversion. Among patients treated with Pegasys alone in the HBeAg-positive and HBeAg-negative studies, 45% and 37%, respectively, had maximum ALT values > 5 x ULN during treatment, as compared to 35% and 18% in those treated with lamivudine alone. These ALT levels may have been accompanied by mild changes in other measures of hepatic function, but without evidence of hepatic decompensation.

During the 6 month follow-up after the end of therapy, ALT elevations > 5 x ULN occurred more frequently in the lamivudine treated patients, 34% and 33% compared to 28% and 20% with Pegasys monotherapy in HBeAg-positive and HBeAg-negative disease, respectively. Two lamivudine-treated patients experienced serious hepatic decompensation following post-treatment flares, with one patient dying. Thus, the timing and nature of ALT flares associated with Pegasys seem to differ from those associated with lamivudine.

Thyroid function

Pegasys treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see section 4.4 Special warnings and precautions for use). The frequencies observed with Pegasys were similar to those observed with other interferons.

Triglycerides
Triglyceride levels are found to be elevated in patients receiving alfa interferon therapy, including Pegasys.

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

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

Dehydration has been reported rarely with Pegasys/ribavirin combination therapy.

Rarely, alfa interferon including Pegasys RBV combination therapy may be associated with pancytopenia, and very rarely aplastic anaemia has been reported.

As with other alfa interferons, serous retinal detachment has been reported with Pegasys/ribavirin combination therapy.

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

Tongue pigmentation has been reported in the post marketing setting.

Pulmonary arterial hypertension (PAH) has been reported with interferon alfa products.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 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 and 630 mcg have been administered in renal cell carcinoma and chronic myelogenous leukaemia clinical trials, respectively. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia consistent with interferon therapy.

No cases of overdose of ribavirin have been reported in clinical trials. Please refer to the approved ribavirin prescribing information.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB11

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 signalling 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 – 36 h after the first dose of Pegasys and the second phase of decline occurs over the next 4 – 16 weeks in patients who achieve a sustained response. Pegasys 180 mcg/week enhances the virion clearance and improves the virological end of treatment responses compared to treatment with standard alfa 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 of 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 – 40 mL/min). The clinical relevance of these findings with pharmacodynamic markers of Pegasys is not known.

Pharmacodynamic effect

The conjugation of PEG reagent (bis-monomethoxypolyethylene glycol) to interferon alfa-2a forms a pegylated interferon alfa-2a. 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 kD PEG moiety define the absorption, distribution and elimination characteristics of Pegasys.

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

Clinical trials

Hepatitis B

Clinical studies have demonstrated that Pegasys monotherapy is effective in the treatment of patients with CHB, 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 CHB who had active viral replication measured by HBV DNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. Study WV16240 recruited patients who were positive for HBeAg, while study WV16241 recruited patients who were negative for HBeAg and positive for anti-HBe. In both studies the treatment duration was 48 weeks, with 24 weeks of treatment-free follow-up. Both

studies compared Pegasys plus placebo vs. Pegasys plus lamivudine vs. lamivudine alone. No HBV-HIV co-infected patients were included in these clinical trials.

Response rates at the end of follow-up for the two studies are presented in Table 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 Chronic Hepatitis B

	HBeAg positive Study WV16240			**HBeAg negative / anti-HBe positive Study WV16241**		
	Pegasys 180 mcg & Placebo (n = 271)	Pegasys 180 mcg & Lamivudine 100 mg (n = 271)	Lamivudine 100 mg (n = 272)	Pegasys 180 mcg & Placebo (n = 177)	Pegasys 180 mcg & Lamivudine 100 mg (n = 179)	Lamivudine 100 mg (n = 181)
HBeAg Sero-conversion	32% [1]	27%	19%	N/A	N/A	N/A
HBV DNA*	32% [2]	34%	22%	43% [5]	44%	29%
ALT Normalisation	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

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.

Chronic hepatitis C: naïve patients

Confirmatory clinical trials

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 IU/mL) and sustained response as one negative sample approximately 6 months after end of therapy.

Table 5: Virological Response in CHC

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

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

The virological responses of patients treated with Pegasys and ribavirin combination therapy 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: SVR in CHC based on Genotype and Viral Load after Pegasys Combination Therapy with Ribavirin

	Study NV15942			**Study NV15801**		
	Pegasys 180 mcg & Ribavirin 800 mg 24 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 24 weeks	Pegasys 180 mcg & Ribavirin 800 mg 48 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 48 weeks	Pegasys 180 mcg & Ribavirin 1000/1200 mg 48 weeks	Interferon alfa-2b 3 MIU & Ribavirin 1000/1200 mg 48 weeks

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

* *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.

Chronic hepatitis C: prior treatment non-responder patients
Study MV17150

In study MV17150, patients who were previous non-responders to peginterferon alfa-2b plus ribavirin therapy were randomised to four different treatments: Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 60 weeks; Pegasys 360 mcg/week for 12 weeks, followed by 180 mcg/week for a further 36 weeks; Pegasys 180 mcg/week for 72 weeks; or Pegasys 180 mcg/week for 48 weeks. All patients received ribavirin (1000 or 1200 mg/day) in combination with Pegasys. The end-of-treatment (EOT) virological response and sustained virological response (SVR) following the 24-week treatment-free period comparing duration of therapy or Pegasys induction dosing are summarised in Table 7. The SVRs following the 24-week treatment-free period from a pooled analysis comparing duration of therapy or Pegasys induction dosing are summarised in Table 8.

Table 7: EOT Virological Response and SVR in Previous Peginterferon alfa-2b/Ribavirin Non-responders

Study MV17150				
	Induction dosing 72 week treatment	Induction dosing 48 week treatment	Standard dosing 72 week treatment	Standard dosing 48 week treatment
	Pegasys 360 mcg 12 weeks then 180 mcg 60 weeks +	Pegasys 360 mcg 12 weeks then 180 mcg 36 weeks +	Pegasys 180 mcg 72 weeks + Ribavirin 1000/1200 mg	Pegasys 180 mcg 48 weeks + Ribavirin 1000/1200 mg

	Ribavirin 1000/1200 mg	Ribavirin 1000/1200 mg		
	n = 317	*n* = 156	*n* = 156	*n* = 313
EOT	31%	33%	31%	28%
SVR	16%[#]*	7%[§]	14%	9%

[#] *A vs. B: 95% confidence interval of 1.36 to 5.67; odds ratio 2.77; p-value 0.0036*
[§] *B vs. C: 95% confidence interval of 0.23 to 1.03; odds ratio 0.49; p-value 0.0494*
**A vs. D: 95% confidence interval of 1.21 to 3.31; odds ratio 2.0; p-value 0.0060*

Table 8: SVR in Previous Peginterferon alfa-2b/Ribavirin Non-responders: Pooled Treatment Comparisons

Study MV17150 (pooled groups)				
	72 week Groups	48 week Groups	360 mcg Groups	180 mcg Groups
	360 mcg 12 weeks then 180 mcg 60 weeks & 180 mcg 72 weeks	360 mcg 12 weeks then 180 mcg 36 weeks & 180 mcg 48 weeks	360 mcg 12 weeks then 180 mcg 60 weeks & 360 mcg 12 weeks then 180 mcg 36 weeks	180 mcg 72 weeks & 180 mcg 48 weeks
	n = 473	*n* = 469	*n* = 473	*n* = 469
SVR	16%*	8%*	13%	10%

** 95% confidence interval of 1.40 to 3.52; odds ratio 2.22; p-value 0.00061*

The SVR rate after 72 weeks treatment was superior to that after 48 weeks. Differences in SVR based on treatment duration and demographics found in study MV17150 are displayed in Table 9.

Table 9: SVR Rates After Treatment with Pegasys and Ribavirin Combination Therapy in Non-responders to Previous Treatment with Peginterferon alfa-2b/Ribavirin

	Peginterferon alfa-2b/ribavirin Non-responders Re-treated for 48 weeks % SVR (responders/total)	**Peginterferon alfa-2b/ribavirin Non-responders Re-treated for 72 weeks** % SVR (responders/total)
Overall SVR for prior non-responder pateints	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 (> 800 000 IU/mL)	7% (25/363)	12% (46/372)
LVL (≤ 800 000 IU/mL)	13% (11/84)	31% (27/86)

HVL = high viral load; LVL = low viral load

HALT-C study

In the HALT-C study, patients with CHC and advanced fibrosis or cirrhosis who had not responded to previous treatment with interferon alfa or peginterferon 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 EOT. The SVR rates varied depending upon the previous treatment regimen. Treatment outcome was poorest among patients who were non-responders to peginterferon in combination with ribavirin, identifying the most difficult to treat subpopulation of non-responder patients. The SVR in this treatment arm of the HALT-C study was comparable with the rate observed in the 48 week treatment arms of study MV17150. Despite higher SVR rates in non-responders to interferon or peginterferon monotherapy, efficacy in these less difficult to treat non-responders remains substantially lower than what is achievable in treatment-naïve patients (refer to Table 10).

Table 10: SVR Rates by Treatment Duration and Non-responder Population

	HALT-C Study				**Study MV17150**
Treatment Duration	Interferon	Peginterferon % SVR	Interferon plus Ribavirin	Peginterferon plus Ribavirin %	Peginterferon plus Ribavirin %

	% SVR (responders/total)	(responders/total)	% SVR (responders/total)	SVR (responders/total)	SVR (responders/total)
48 weeks	27% (70/255)	34% (13/38)	13% (90/692)	11% (7/61)	8% (38/469)
72 weeks	-	-	-	-	16% (74/473)

Chronic hepatitis C: prior treatment relapser patients
In a study in predominantly genotype 1 CHC patients who had relapsed after 48 weeks of combination treatment with peginterferon 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 SVR was 42% for patients treated with Pegasys and ribavirin combination therapy for 72 weeks.

In an open-label study in genotype 2 and 3 CHC 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 SVR rate was 64%.

HIV-HCV co-infection
In study NR15961, 860 HIV-HCV co-infected patients were randomised 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 SVR for the three treatment groups are summarised for all patients and by genotype in Table 11.

Table 11: SVR in HIV-HCV Co-infected Patients (Study NR15961)

	Pegasys 180 mcg + Placebo 48 weeks	**Pegasys 180 mcg + Ribavirin 800 mg 48 weeks**	**Interferon alfa-2a 3 MIU + 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 3 MIU ribavirin 800 mg: 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*

A subsequent study (NV18209) in patients co-infected with HCV genotype 1 and HIV compared Pegasys 180 mcg/week and either ribavirin 800 mg or 1000 mg (<75 kg)/1200 mg (≥75 kg) daily for 48 weeks. The results are reported in Table 12 and showed that the study was not powered for efficacy considerations.

Table 12: SVR in HIV-HCV Co-infected Patients (Study NV18209)

	Pegasys 180 mcg + Ribavirin 800 mg 48 weeks (*n* = 138)	**Pegasys 180 mcg + Ribavirin 1000/1200 mg 48 weeks** (*n* = 277)
Completed	55/138 (40 %)	119/277 (43 %)
% SVR (responders/total)	19 % (26/138)	22 % (60/277)

Odds Ratio (95% CI) = 1.17 (0.69 – 1.98), p-value = 0.56

The safety profiles in both ribavirin groups were consistent with the known safety profile of Pegasys plus ribavirin combination treatment and not indicative of any relevant differences, with the exception of a slight increase in anaemia in the high dose ribavirin arm.

5.2 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 CHB were similar to those for patients with CHC.

Absorption

The absorption of Pegasys is sustained with peak serum concentrations reached 72 – 96 h after dosing. Serum concentrations are measurable within 3 – 6 h of a single, subcutaneous injection of Pegasys 180 mcg. Within 24 h, 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.

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 – 14 L after intravenous dosing in humans. Based on studies in rats, the medicine is distributed to the liver, kidney, and bone marrow as well as being highly concentrated in the blood.

Metabolism

Metabolism is the main clearance mechanism for Pegasys. The metabolic profile of Pegasys is not fully characterised. 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 metabolised.

Elimination

After intravenous administration, the terminal half-life of Pegasys in healthy subjects is approximately 60 h compared with values of 3 – 4 h for standard interferon. The terminal half-life after subcutaneous administration in patients is longer with a mean value of 160 h (84 – 353 h). 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 CHC after once weekly dosing of Pegasys. The pharmacokinetic parameters of Pegasys are

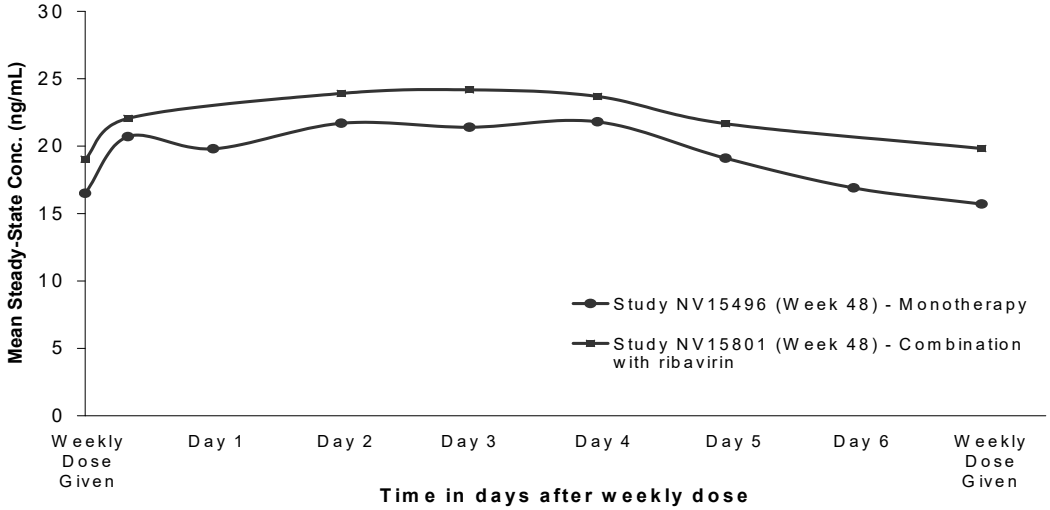
given in Table 13 for healthy subjects receiving a single subcutaneous injection of 180 mcg of Pegasys and for patients with CHC receiving 48 weeks of 180 mcg of Pegasys once weekly.

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 (*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 CHC, steady state serum concentrations increase 2- to 3-fold compared with single-dose values and reach steady state within 5 – 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 h) (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)



Pharmacokinetics in special populations

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 haemodialysis (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, but peak concentrations were similar in those older and younger than 62 years. Based on exposure, pharmacodynamic response, and tolerability, a lower starting dose of Pegasys is not needed in the geriatric patient (see section 4.2 Dose and method of administration).

Non-cirrhotic and cirrhotic patients

The pharmacokinetics of Pegasys were similar between healthy subjects and patients with CHB or CHC. 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.

5.3 PRECLINICAL SAFETY DATA

The preclinical toxicity studies conducted with Pegasys were limited due to species specificity of interferons. Acute and chronic toxicity studies have been carried out in cynomolgus monkeys, and the findings observed in peginterferon 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 anaemia, the severity of which was greater than that produced by either active substance alone.

Carcinogenicity

Pegasys has not been tested for its carcinogenic potential.

Mutagenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

It is inappropriate to mix Pegasys with other products.

6.3 SHELF LIFE

48 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Store in the refrigerator at 2 – 8 °C.

Do not freeze or shake.

Store in the original package to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Pegasys 180 mcg prefilled disposable glass syringe Pack of 4

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

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

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.

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicines should be returned to a pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Pharmacy Retailing (NZ) Ltd
t/a Healthcare Logistics
PO Box 62027 Sylvia Park
Auckland 1644
New Zealand
Telephone: (09) 918 5100

9. DATE OF FIRST APPROVAL

7 February 2003

10. DATE OF REVISION OF THE TEXT

30 May 2022

Summary of Changes Table

Section Changed	Summary of new information
8.0	Change of contact details due to sponsorship change.