Pegasys®

Peginterferon alfa-2a

Recombinant peginterferon alfa-2a

COMPOSITION

Active substance

Peginterferon alfa-2a 135/180 µg with a mean molecular weight of approximately 60,000 daltons. Peginterferon alfa-2a is a recombinant interferon alfa-2a produced by genetic engineering from *Escherichia coli* conjugated to monomethoxy polyethylene glycol.

Excipients

Each vial contains sodium chloride, polysorbate 80, sodium acetate, acetic acid, benzyl alcohol 10.0 mg, water q.s. 1.0 ml of solution.

Each prefilled syringe contains sodium chloride, polysorbate 80, sodium acetate, glacial acetic acid; preservative: benzyl alcohol 5.0 mg, water for injection to 0.5 ml.

One prefilled pen contains sodium chloride, polysorbate 80 (produced from genetically modified maize); sodium acetate; glacial acetic acid; preservative: benzyl alcohol (5.0 mg); water for injection to 0.5 ml.

GALENICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

Rubber-stoppered vials containing 135 or 180 µg pegylated interferon alfa-2a in 1 ml.

Prefilled syringes containing 135 or 180 µg pegylated interferon alfa-2a in 0.5 ml.

Prefilled pens (ProClick™) containing 135 or 180 µg pegylated interferon alfa-2a in 0.5 ml, respectively.

Pegasys is a clear, colourless to faintly yellow solution.

INDICATIONS AND POTENTIAL USES

Chronic hepatitis B

Treatment of chronic hepatitis B in adults. Patients must not have decompensated liver disease, and chronic hepatitis B must be confirmed by serum markers (elevated transaminases, HBsAg, HBV DNA). Histological confirmation of the diagnosis should normally be obtained. Pegasys was shown to be effective in HBeAg-positive and HBeAg-negative chronic hepatitis B in studies that also included patients with grade 3 or 4 fibrosis* (see *Warnings and precautions*).

* Advanced fibrosis or cirrhosis (Metavir or Knodell score)

Chronic hepatitis C

Treatment of chronic hepatitis C in adults.

The combination of Pegasys and ribavirin is indicated in treatment-naïve patients and patients who have not responded to previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin. Demonstrated efficacy included HCV patients coinfected with clinically stable HIV.

In previously treated patients the interval between the end of the previous treatment and the restarted treatment in the main study was at least 12 weeks and on average more than one year (see *Properties and effects*).

Patients must not have decompensated liver disease and chronic hepatitis C must be confirmed by serum markers (anti-HCV antibodies, HCV RNA). Histological confirmation of the diagnosis should normally be obtained.

When Pegasys is used in combination with ribavirin, the prescribing information on ribavirin should also be consulted.

Pegasys is also indicated for the treatment of chronic hepatitis infection in combination with approved direct-acting anti-HCV agents (DAAs) in accordance with the indications and dosage recommendations described in the prescribing information for the products concerned. Please see the complete prescribing information of the DAA for further information on dosage, administration, safety and efficacy.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin. Monotherapy has not been tested in patients with normal transaminases.

DOSAGE AND ADMINISTRATION

Treatment should be started only by physicians experienced in the treatment of hepatitis B or C. Interferons can cause unusual tiredness. If self-injected by the patient, the product should be administered at bedtime.

When Pegasys is used in combination with other direct-acting anti-HCV agents (DAAs), please see the complete prescribing information for the DAAs concerned.

Standard dosage

Chronic hepatitis B

The recommended treatment regimen for patients with chronic hepatitis B is 180 µg once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh. Available data on the comparative efficacy of 90 µg and 180 µg doses of Pegasys over periods of 24 and 48 weeks in HBeAg-positive patients show 180 µg for 48 weeks to be more effective than the other treatment arms (see *Properties and effects*). With respect to extending treatment beyond 48 weeks, only limited data are available for HBeAg-negative patients (primarily genotype D) (see *Properties and effects*). Combination of

Pegasys and lamivudine offered no advantage over Pegasys monotherapy (see *Properties and effects*).

Chronic hepatitis C

For treatment with Pegasys alone or in combination with ribavirin it is recommended that 180 µg be given once weekly by subcutaneous injection into the skin of the abdomen or thigh in combination with oral ribavirin or as monotherapy.

The dose of ribavirin for use in combination with Pegasys depends on viral genotype: for genotype 2 or 3 the dose is 800 mg p.o./day, for genotype 1 it is 1000–1200 mg p.o./day, depending on body weight (see Table 1).

Ribavirin should be taken with meals.

Duration of treatment in chronic hepatitis C

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype.

Patients infected with HCV genotype 1 who have detectable HCV RNA at week 4 should receive 48 weeks of therapy, regardless of pretreatment viral load. 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 until week 24. However, a 24-week total treatment duration may be associated with a higher risk of relapse than a 48-week 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 until week 24 should be considered with even more caution since the limited data available suggest that this may negatively impact sustained virological response (SVR) (see Table 1 and *Properties and effects, Clinical efficacy*).

Patients infected with HCV genotype 2 or 3 in whom HCV RNA is still detectable after 4 weeks should receive 24 weeks of therapy, regardless of pretreatment viral load. A 16-week treatment may be considered in selected patients infected with genotype 2 or 3 who have a low baseline viral load and are HCV-negative after 4 weeks of treatment. Overall, the relapse rate with a 16-week treatment may be higher than on treatment for 24 weeks (see *Properties and effects, Clinical efficacy*). In these patients the tolerability of combined therapy and additional clinical or prognostic factors such as the degree of liver fibrosis should be taken into account when considering deviations from the standard treatment duration. Increased caution with regard to a shortened treatment duration is required in patients with genotype 2 or 3 infection and a high baseline viral load who become HCV-negative within 4 weeks, since this may have considerable adverse repercussions on sustained virological response (see *Properties and effects, Clinical efficacy*).

Only limited data are available on patients infected with genotype 5 or 6; combination treatment with 1000/1200 mg of ribavirin for 48 weeks is therefore recommended.

Table 1 Dosage recommendations for combination therapy in HCV patients

Genotype	Pegasys dose	Ribavirin dose	Duration
Genotype 1 LVL with RVR*	180 µg	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR*	180 µg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 4 with RVR*	180 µg	<75 kg = 1000 mg ≥75 kg = 1200 mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR*	180 µg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks
Genotype 2 or 3 LVL with RVR**	180 µg	800 mg	16 weeks or 24 weeks
Genotype 2 or 3 HVL with RVR**	180 µg	800 mg	24 weeks
Genotype 2 or 3 without RVR**	180 µg	800 mg	24 weeks

* RVR = rapid virological response, HCV RNA undetectable at week 4 and HCV RNA undetectable at week 24

** RVR = rapid virological response, HCV RNA-negative within 4 weeks

LVL = ≤800,000 IU/ml; HVL = >800,000 IU/ml

Previous treatment failure in chronic hepatitis C

The recommended dosage of Pegasys in combination with ribavirin is 180 µg once weekly by subcutaneous injection in the abdomen or thigh. Ribavirin should be taken with meals. Patients weighing <75 kg receive 1000 mg and patients weighing ≥75 kg receive 1200 mg ribavirin. The recommended treatment duration is 72 weeks for patients with genotype 1 or 4 and 48 weeks for those with genotype 2 or 3.

The recommended duration of Pegasys monotherapy is 48 weeks, regardless of viral genotype.

HCV/HIV coinfection

The recommended dosage of Pegasys – alone or in combination with 800 mg ribavirin – is 180 µg by once-weekly subcutaneous injection for 48 weeks, regardless of viral genotype. The safety and efficacy of combination therapy with ribavirin at doses of more than 800 mg daily and a treatment duration of less than 48 weeks have not been studied.

Predictive value of virological response in hepatitis C or non-response in treatment-naïve patients

Discontinuation of treatment should be considered in genotype 1 patients who fail to respond within 12 weeks to treatment with Pegasys alone or in combination with

ribavirin (no fall in HCV RNA to less than 50 IU/ml [equivalent to 100 copies/ml] or by a factor of at least 100 [2 $\log_{10}$] from the baseline value).

Ninety-three out of 96 patients with genotype 2/3 responded to treatment after 12 weeks. Patients treated with Pegasys who failed to achieve an early virological response within 12 weeks of treatment were highly unlikely (<5%) to achieve a sustained virological response with continued therapy (see Table 2).

Table 2 Predictive value of week 12 virological response with the recommended dosage regimen in combination therapy

	Negative			**Positive**		
	No response after 12 weeks	No sustained response	Predictive value	Response after 12 weeks	Sustained response	Predictive value
Genotype 1 (N=569)	102	97	95% (97/102)	467	265	57% (265/467)
Genotypes 2 and 3 (N=96)	3	3	100% (3/3)	93	81	87% (81/93)

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

Predictive value of response or non-response in prior non-responders

Discontinuation of treatment should be considered in prior non-responders who do not respond within 12 weeks to Pegasys/ribavirin combination therapy.

In non-responders treated for 72 weeks in the clinical study, the best on-treatment predictor of response was viral suppression at week 12 (undetectable HCV RNA, defined as HCV RNA <50 IU/ml). The negative predictive value of viral suppression at week 12 was 96% (324/339) and the positive predictive value was 57% (57/100).

Dose adjustment in the event of undesirable effects

General disorders

If the dose must be adjusted because of moderate to severe undesirable effects (clinical or laboratory findings), an initial reduction to 135 µg is usually sufficient. However, a reduction to 90 or 45 µg may be necessary in some cases. As such dose reductions to 90 or 45 µg cannot be administered using the prefilled pen, the reduced dose must be

administered using the prefilled syringe. A return to the initial dosage level may be contemplated once the undesirable effects have abated (see *Warnings and precautions* and *Undesirable effects*).

Hematology (see also Table 3)

Dose reduction is recommended if the neutrophil count is below 750/mm^3. In patients with absolute neutrophil counts below 500/mm^3 treatment should be temporarily stopped until the absolute neutrophil count has risen to above 1000/mm^3. In such cases treatment with Pegasys should be restarted at a dose of 90 µg and neutrophil counts monitored.

Dose reduction to 90 µg is recommended if the platelet count falls below 50,000/mm^3. It is recommended that treatment be stopped if the platelet count falls below 25,000/mm^3.

The following steps, in particular, are recommended for management of treatment-emergent anemia in hepatitis C: ribavirin should be reduced to 600 mg/day (200 mg in the morning and 400 mg in the evening) if either of the following applies: (1) a patient without significant cardiovascular disease experiences a fall in hemoglobin to <10 g/dl and ≥8.5 g/dl, or (2) a patient with stable cardiovascular disease experiences a fall in hemoglobin by ≥2 g/dl during any 4 weeks of treatment. A return to original dosing is not recommended. Ribavirin should be discontinued if either of the following applies: (1) a patient without significant cardiovascular disease experiences a confirmed fall in hemoglobin to <8.5 g/dl; (2) a patient with stable cardiovascular disease maintains a hemoglobin value <12 g/dl despite 4 weeks on a reduced dose. Once normal values are restored, ribavirin may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to original dosing is not recommended.

Table 3 Dose adjustment for undesirable effects (for further guidance see also text above)

	Reduce ribavirin to 600 mg	**Discontinue ribavirin**	**Reduce Pegasys to 135/90/45 µg**	**Discontinue or suspend Pegasys**	**End combination or monotherapy**
Absolute neutrophil count			<750/mm^3	<500/mm^3	
Platelet count			<50,000/mm^3 >25,000/mm^3	<25,000/mm^3	<25,000/mm^3
Hemoglobin – no cardiac disease	<10 g/dl and ≥8.5 g/dl	<8.5 g/dl			
Hemoglobin – stable cardiac	Decrease ≥2 g/dl for	<12 g/dl despite 4 weeks at			

disease	4 weeks	reduced dose			

In case of intolerance to ribavirin, Pegasys should be continued as monotherapy (see *Dosage and administration*).

When Pegasys is to be used in combination with ribavirin, please also consult the prescribing information on ribavirin with regard to dose adjustment for adverse reactions.

Liver function

Fluctuations in pathological liver function test results are common in chronic hepatitis. As with other alfa interferons, increases in ALT above baseline levels have been observed during treatment with Pegasys, even in patients with virological improvement. In the event of progressive ALT increases above baseline in hepatitis C patients, the dose should be reduced initially to 135 µg. Treatment should be stopped if ALT continues to rise despite dose reduction or if a raised bilirubin concentration or hepatic decompensation is also observed simultaneously (see *Warnings and precautions*).

For patients with chronic hepatitis B, transient flares of ALT levels sometimes exceeding 10 times the upper limit of normal are not uncommon, and may reflect immune clearance (seroconversion). 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, the usual treatment can be resumed after ALT normalisation (see *Warnings and precautions*).

Special dosage instructions

Patients under 18 years

The safety and efficacy of Pegasys have not yet been established in these patients.

Patients with renal impairment

In patients with end-stage renal disease, a starting dose of 135 µg should be used. Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of Pegasys should be made in the event of adverse reactions (see *Properties and effects* and *Clinical efficacy*).

In patients with end-stage renal disease undergoing hemodialysis, Pegasys clearance is reduced by 25–45%, and first administration of a 135 µg dose results in exposure similar to that with a 180 µg dose in patients with normal renal function.

It is recommended that Pegasys be used with caution in such patients, that the patients be closely monitored, and that the dose of Pegasys be reduced if undesirable effects occur.

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

Patients with 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 evaluated in patients with decompensated cirrhosis (e.g. Child-Pugh B or C or bleeding esophageal varices) (see *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
Serum bilirubin (mg/dl)	<2	1
	2.0–3	2
	>3	3
(SI unit = µmol/l)	<34	1
	34–51	2
	>51	3
Serum 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 (1996)

CONTRAINDICATIONS

– Hypersensitivity to the active substance, to alfa interferons, or to any of the excipients

– Autoimmune chronic hepatitis

- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- Initiation of Pegasys is contraindicated in HCV/HIV-coinfected patients with cirrhosis and a Child-Pugh score >5, except if only due to indirect hyperbilirubinemia caused by drugs such as atazanavir and indinavir and if all the other scores entering into the Child-Pugh classification are equal to 1
- Newborn infants and children under the age of 3 years, as the product contains benzyl alcohol
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see *Warnings and precautions*)
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder, mainly depression
- Pregnancy and lactation

When Pegasys is to be used in combination with ribavirin, please also consult the prescribing information on ribavirin with regard to contraindications.

When Pegasys is used in combination with other direct-acting anti-HCV agents (DAAs), please see the complete prescribing information for the DAAs concerned.

WARNINGS AND PRECAUTIONS

Psychiatric symptoms and central nervous system (CNS)

Serious psychiatric side effects can occur during treatment with interferons, including Pegasys. Depression, suicidal ideation and suicide, aggressive behaviour, **sometimes directed against others, aggressive tendencies towards others (homicidal ideation)** and confusion have been observed in patients with or without a psychiatric history.

Pegasys must therefore be used with caution in patients with a history of depression, and physicians must monitor all patients for signs of depression. Before starting treatment with Pegasys, the physician should inform patients about the possible development of depression and urge them to report any symptoms of depression without delay. In severe cases treatment withdrawal should be considered and the patient referred for psychiatric treatment (see *Undesirable effects*).

Caution is advised when administering Pegasys to pediatric patients with previous or concomitant psychological disturbances and the patients should be monitored for signs of depression.

Cardiovascular system

Hypertension, supraventricular arrhythmias, chest pain and myocardial infarction have been linked to treatment with alfa interferons.

As heart diseases may be exacerbated by ribavirin-induced anemia, Pegasys and ribavirin should be used with caution in patients with pre-existing severe or unstable cardiac disease. Patients should be examined before the start of treatment and appropriately

monitored during treatment. If there is any deterioration of cardiovascular status, ribavirin therapy should be suspended or discontinued (see *Dosage and administration*).

It is recommended that patients with pre-existing cardiac disease have an electrocardiogram prior to initiation of Pegasys therapy.

Liver function

In patients developing signs of hepatic decompensation during treatment, discontinuation of Pegasys should be considered and the patients closely monitored.

Hepatitis C

As with other alfa interferons, ALT elevation above baseline has been observed during treatment with Pegasys, even in patients with a virological response. Treatment should be stopped if there is a progressive and clinically significant increase in ALT levels or a concomitant increase in bilirubin despite dose reduction (see *Undesirable effects*).

Hepatitis B

Unlike in chronic hepatitis C, disease exacerbations during therapy are not uncommon in chronic hepatitis B and are characterised by transient and potentially marked increases in serum ALT. In clinical trials with Pegasys in HBV, sudden increases in transaminase levels have been accompanied by mild changes in other measures of hepatic function but without evidence of hepatic decompensation. In approximately half the patients whose transaminase levels had risen to more than 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

See *Dosage and administration.*

Hypersensitivity

Severe acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alfa interferon therapy. In such cases, treatment should be stopped and appropriate medical measures immediately instituted. Transient rashes do not necessitate interruption of treatment.

Autoimmune disease

Exacerbations of pre-existing autoimmune disease have been observed during treatment with alfa interferon. Pegasys must be used with caution in patients with autoimmune disease.

Hematology

Caution is indicated if Pegasys is to be used in patients with a baseline neutrophil count $<1500/mm^3$, platelet count $<75,000/mm^3$ or hemoglobin level <10 g/dl (anemia).

Regular hematological monitoring is recommended before and during treatment.

Fever

Fever together with flu-like symptoms is often reported during interferon therapy. However, other causes must be excluded if the fever persists, particularly in neutropenic patients. 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 interferon therapy should be considered.

Ocular changes

Ophthalmological disorders such as retinal hemorrhages, cotton-wool spots, papilledema, optic neuropathy or retinal artery or vein occlusion have been reported in rare cases after treatment with alfa interferons and may result in loss of vision. A baseline eye examination is recommended. Any patient reporting decreased visual acuity or visual field loss must undergo regular ophthalmic examinations. As ocular manifestations of this kind may also occur in conjunction with other disease states, regular ophthalmic examinations in patients with diabetes or hypertension are recommended during treatment with Pegasys.

Pegasys therapy should be discontinued in patients who develop new or worsening ophthalmological disorders.

Pulmonary changes

As with other alfa interferons, pulmonary abnormalities such as dyspnea, pulmonary infiltrates, pneumonia and pneumonitis, with possible fatal outcome, have been described during treatment with Pegasys. In the event of persistent or unexplained pulmonary infiltrates or pulmonary dysfunction, treatment must be stopped.

Patients under 18 years

Pegasys has not been adequately studied in patients under 18 years of age.

Miscellaneous

Exacerbation or onset of psoriasis has been observed in rare cases during treatment with alfa interferons. Pegasys must be used with caution in existing psoriasis. Treatment should be stopped if psoriatic lesions appear or become worse.

Patients treated with Pegasys should avoid alcohol or limit their alcohol intake to a maximum of 20 g daily.

An increased risk of peripheral neuropathy has been observed in patients with chronic hepatitis B on combined treatment with telbivudine and pegylated interferon alfa-2a (see *Interactions*). Use of this combination is therefore not currently recommended.

Transplantation

The safety and efficacy of Pegasys and ribavirin treatment 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.

HCV/HIV-coinfected patients

Patients coinfected with HIV and receiving highly active antiretroviral therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should therefore be exercised when adding Pegasys and ribavirin to HAART therapy (see prescribing information for ribavirin).

HCV/HIV-coinfected patients with advanced cirrhosis receiving HAART may also be at increased risk of hepatic decompensation and possibly death if treated with ribavirin in combination with interferons, including Pegasys. During treatment, coinfected patients should be closely monitored, for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function; Child-Pugh score >6 (see *Contraindications*). The Child-Pugh scoring may be affected by factors related to treatment (i.e. indirect hyperbilirubinemia caused by drugs such as atazanavir and indinavir) and not necessarily attributable to hepatic decompensation. Treatment with Pegasys should be discontinued immediately in patients with Child-Pugh score >6 not related to indirect hyperbilirubinemia.

Chronic hepatitis C in patients with normal transaminases

Efficacy in patients with normal transaminases is based on the surrogate marker-sustained virological response (HCV RNA <50 IU/ml 24 weeks after the end of treatment). The benefit of treatment in these patients must be individually weighed against a reduced quality of life during treatment and the risks (see *Undesirable effects*).

Growth and development (pediatric patients)

Pediatric patients treated with Pegasys + ribavirin combination therapy showed a delay in weight and height increases after 48 weeks of therapy compared with baseline. Both weight and height for age z-scores as well as the percentiles of the normative population for body weight and height decreased during treatment. At the end of 2 years follow-up after treatment, most patients had returned to baseline normative growth curve percentiles for weight and height (mean weight percentile was 64% at baseline and 60% at 2 years post-treatment; mean height percentile was 54% at baseline and 56% at 2 years post-treatment). At the end of treatment, 43% of patients experienced a weight percentile decrease of 15 percentiles or more, and 25% experienced a height percentile decrease of 15 percentiles or more on the normative growth curves. At 2 years post-treatment, 16% of patients remained 15 percentiles or more below their baseline weight curve and 11% remained 15 percentiles or more below their baseline height curve.

Laboratory tests

It is recommended that routine hematological and biochemical parameters be determined in every patient before starting treatment with Pegasys.

The following figures may be taken as baseline values for initiating treatment:

– platelet count $\geq$90,000/mm^3

– absolute neutrophil count ≥1500/mm^3

– thyrotropin (thyroid-stimulating hormone, TSH) and T4 within normal range or adequately controlled thyroid function.

In HCV/HIV-coinfected patients the following values may be taken as a guideline:

– $CD4^+$ cell count ³ 200/µl, regardless of HIV-1 RNA concentration, or

– $CD4^+$ cell count ³ 100/µl but <200/µl, and HIV-1 RNA concentration <5000 copies/ml in Amplicor HIV-1 Monitor Test, v1.5.

Blood counts should be performed two and four weeks and biochemical tests four weeks after the start of treatment. Additional tests should then be performed at regular intervals (at least every 4 weeks) during treatment.

In clinical studies with Pegasys, decreases in both the white blood cell count and absolute neutrophil count were generally observed within the first two weeks of treatment (see *Undesirable effects*). Further decreases after this time were rare.

In clinical studies with Pegasys the fall in absolute neutrophil count was reversible on reducing the dose or stopping treatment.

Treatment with Pegasys was associated with a decrease in platelet count, though this returned to pretreatment levels within the observation period after the end of treatment. In some cases, dose modification may be necessary (see *Dosage and administration*).

In clinical trials, anemia (hemoglobin <10 g/dl) was observed in 15% of patients treated for 48 weeks with Pegasys 180 µg and ribavirin 1000/1200 mg and in 3% of patients treated for 24 weeks with Pegasys 180 µg and ribavirin 800 mg (see *Undesirable effects*). The maximum drop in hemoglobin generally occurred within 4 weeks of initiation of ribavirin therapy.

Pancytopenia (a marked decrease in the red cell, neutrophil and platelet counts) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the coadministration 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 *Interactions*).

If there is any deterioration of cardiovascular status, ribavirin therapy should be suspended or terminated (see *Dosage and administration*).

Combination of Pegasys with ribavirin in chronic hepatitis C patients not responding to prior treatment has not been adequately studied in patients who discontinued prior therapy for hematological adverse events. Before treating such patients, physicians should carefully weigh the risks against the benefits of retreatment.

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

Thyroid dysfunction or exacerbation of existing thyroid disorders has been described during treatment with alfa interferons, including Pegasys. Thyrotropin (thyroid-stimulating hormone, TSH) levels should be measured before starting treatment with Pegasys in chronic hepatitis. Treatment with Pegasys may be started if TSH can be maintained within the normal range by pharmacological means. It is advisable to monitor TSH levels during the course of treatment if the patient develops clinical signs of possible thyroid dysfunction. If thyroid dysfunction is present, treatment with Pegasys may be continued if TSH can be maintained within the normal range by pharmacological means.

Hyperglycemia, hypoglycemia 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 receive either Pegasys monotherapy or Pegasys/ribavirin combination therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Pegasys or Pegasys/ribavirin therapy.

When Pegasys is used in combination with other direct-acting anti-HCV agents (DAAs), please see the complete prescribing information for the DAAs concerned.

Use of peginterferon as long-term maintenance monotherapy (off-label use)

In a randomised, controlled US study (HALT-C) of HCV non-responders with varied degrees of fibrosis treated for 3.5 years with 90 µg/week Pegasys monotherapy, no significant reduction was observed in the rate of fibrosis progression or related clinical events.

INTERACTIONS

Administration of 180 µg of Pegasys once weekly to healthy male subjects for four weeks had no effect on the pharmacokinetics of mephenytoin (CYP 2C19), dapsone (CYP 3A4), debrisoquin (CYP 2D6) or tolbutamide (CYP 2C9). Pegasys therefore has no relevance to the *in vivo* metabolic activities of the isoenzymes cytochrome P450 3A4, 2C9, 2C19 or 2D6.

In the same study a 25% increase was observed in the AUC of theophylline (marker of cytochrome P450 1A2 activity), indicating moderate inhibition of cytochrome P450 1A2 by peginterferon alfa-2a. In patients taking theophylline concomitantly with Pegasys, theophylline serum concentrations should be monitored and the theophylline dosage adjusted accordingly. Maximal interaction between theophylline and Pegasys can be expected after four weeks of treatment with Pegasys.

Interferons have been observed to increase neurotoxic, hematotoxic and cardiotoxic effects of previously or concomitantly administered drugs. Similar interactions cannot therefore be excluded with peginterferon alfa-2a.

Results of pharmacokinetic investigations in the context of phase III trials showed no interactions between Pegasys and lamivudine in chronic hepatitis B or between Pegasys and ribavirin in chronic hepatitis C.

In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95 mg; range 30 mg to 150 mg), mean methadone levels during the four-week treatment with Pegasys 180 µg s.c. once weekly were 10% to 15% higher than before the start of treatment with Pegasys. The clinical significance of this finding is unknown; nonetheless, patients should be monitored for undesirable effects of methadone.

HCV/HIV-coinfected patients

No evidence of interaction was observed in 47 HCV/HIV-coinfected patients included in a 12-week pharmacokinetic substudy examining the effects of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (lamivudine and zidovudine or stavudine). Plasma exposure to ribavirin did not appear to be affected by concomitant administration of nucleoside reverse transcriptase inhibitors (NRTIs).

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

A non-Roche clinical study of telbivudine 600 mg daily combined with pegylated interferon alfa-2a 180 µg by weekly subcutaneous administration indicates an association with an increased risk of peripheral neuropathy. The mechanism behind these events is not known. Such a risk cannot be excluded with other interferons (pegylated or standard). Moreover, the benefit of combining telbivudine with interferon alfa (pegylated or standard) is not currently established.

Azathioprine: Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of peginterferon alfa-2a and ribavirin concomitantly with azathioprine should be avoided.

In individual cases where the benefit of coadministering ribavirin with azathioprine warrants the potential risk, close hematological monitoring is recommended during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped (see *Warnings and precautions*).

PREGNANCY AND LACTATION

There are no data on the use of peginterferon alfa-2a in pregnant women. Studies in animals have shown reproductive toxicity (see *Preclinical data*) and the potential risk for humans is unknown. Pegasys must not be administered during pregnancy (see *Contraindications, Properties and effects* and *Preclinical data*).

Patients should take effective contraceptive measures during treatment with Pegasys.

Significant teratogenic and/or embryotoxic effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin is contraindicated in pregnant women and in men whose partner is pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients being treated with ribavirin.

Any method of contraception can fail. It is therefore extremely important that women of childbearing age and their partners use two forms of effective contraception simultaneously, during treatment and for six months after the end of treatment.

Please refer to the ribavirin prescribing information (especially *Contraindications, Warnings and precautions* and *Pregnancy and lactation*) when Pegasys is used in combination with ribavirin.

It is not known whether Pegasys or any of its ingredients is excreted in breast milk. It must therefore be decided whether breast-feeding or treatment should be stopped, depending on the therapeutic importance of the drug to the mother.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies of effects on the ability to drive or operate machinery. The undesirable effects of Pegasys must be borne in mind. Patients developing dizziness, confusion, drowsiness or fatigue should be warned to avoid driving or operating machinery.

UNDESIRABLE EFFECTS

Experience from clinical studies

The frequency and severity of reported undesirable effects in patients treated with Pegasys are similar to those observed during treatment with interferon alfa-2a. However, hematological side effects are more frequent with Pegasys than with Roferon-A.

Chronic hepatitis B

In clinical trials of 48-week treatment and 24-week follow-up, the safety profile for Pegasys in chronic hepatitis B was similar to that seen in chronic hepatitis C, although the frequency of reported adverse events, including – significantly – depression, was markedly less in chronic hepatitis B (see Table 5). Eighty-eight percent of Pegasys treated patients experienced adverse events, as compared to 53% of patients in the lamivudine comparator group. The rate of serious adverse events was 6% in the Pegasys group and 4% in the lamivudine group. Five percent of patients withdrew from Pegasys treatment because of adverse events or laboratory abnormalities, while fewer 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

HCV-infected patients with normal ALT levels

The safety profile of Pegasys in combination with ribavirin in HCV-infected patients with normal ALT levels matched the profile previously determined in HCV-infected patients with elevated ALT levels. Analogously, 24-week was better tolerated than 48-week combination therapy (see Table 5, under Hepatitis C, column *HCV/n-ALT*).

Patients with non-response to prior treatment of chronic hepatitis C

In a clinical trial of 72 or 48 weeks in non-responders to prior pegylated interferon alfa-2b/ribavirin, 12% of patients discontinued peginterferon alfa-2a and 13% ribavirin therapy because of adverse events or laboratory abnormalities in the 72-week study arms, compared to 6% and 7%, respectively, in the 48-week arms. Similarly, the withdrawal rates on peginterferon alfa-2a and ribavirin in patients with cirrhosis were higher in the 72-week study arms (13% and 15%) than in the 48-week arms (6% and 6%). Patients who had withdrawn from previous therapy because of hematological toxicity were excluded from this trial.
Another trial enrolled patients with advanced fibrosis or cirrhosis (Ishak score 3 to 6) who had not responded to previous treatment. Their platelet count on inclusion in the study was as low as 50,000/mm^3 and treatment lasted 48 weeks. Because of the high prevalence of advanced cirrhosis/fibrosis and the low baseline platelet counts among patients in this study, hematological abnormalities were observed in the first 20 weeks with the following frequencies: hemoglobin <10 g/dl in 26.3%, absolute neutrophil count (ANC) <750/mm^3 in 30% and platelet count <50,000/mm^3 in 13% (see *Warnings and precautions*).

HCV/HIV-coinfected patients

In HCV/HIV-coinfected patients, clinical adverse event profiles with Pegasys (alone or in combination with ribavirin) were similar to those in patients infected with HCV alone (see Tables 4 and 5). Treatment with Pegasys was associated in the first four weeks with a reduction in absolute CD4$^+$ cell count, but not a percentage decrease in CD4$^+$ cells. The decline in CD4$^+$ cell count was reversible after dose reduction or treatment cessation. Use of Pegasys had no perceptible negative impact on the control of HIV viremia during therapy or follow-up. Limited safety data (N=31) are available on coinfected patients with CD4$^+$ cell counts <200/µl (see Table 5, under Hepatitis C, column *HCV/HIV*).

Table 4 Summary of safety assessments of various treatment regimens for combination therapy with Pegasys and ribavirin in HCV and HCV/HIV patients

	HCV monoinfection **Combination therapy with ribavirin**	**HCV monoinfection** **Combination therapy with ribavirin**	**HCV/HIV coinfection** **Combination therapy with ribavirin**

	Pegasys 180 µg + ribavirin 800 mg 24 weeks	Pegasys 180 µg + ribavirin 1000/1200 mg 48 weeks	Pegasys 180 µg + ribavirin 800 mg 48 weeks
Serious undesirable effects	3%	11%	17%
Anemia (hemoglobin <10 g/dl)	3%	15%	14%
Premature withdrawals due to undesirable effects	4%	10%	12%
Premature withdrawals due to laboratory abnormalities	1%	3%	3%
Ribavirin dose modification	19%	39%	37%

Table 5 summarises the undesirable effects that occurred most frequently (≥10%) in the clinical studies with Pegasys alone or in combination with ribavirin over 24 or 48 weeks in patients with chronic hepatitis B or C.

Table 5 Adverse events (≥10% incidence in all treatment groups) for HBV, HCV and HCV/HIV patients

	Hepatitis B	**Hepatitis C**							
	Studies*, ** WV16240 + WV16241	Studies NV15801 + NV15489 + NV15495 + NV15496 + NV15497 **HCV**	Study NV15942 **HCV**	Studies NV15801 + NV15942 **HCV**	Study NR16071 **HCV/n-ALT**		Study NV15801 **HCV**	Study NR15961 **HCV/HIV**	Study MV17150 **HCV peginterferon alfa-2b non-responders:**
Body system	Peginter-feron alfa-2a	Peginter-feron alfa-2a	Peginter-feron alfa-2a	Peginter-feron alfa-2a	Peginterferon alfa-2a		IFN alfa-2b	Peginter-feron alfa-2a	Peginterferon alfa-2a
	180 µg	180 µg	180 µg + ribavirin 800 mg	180 µg + ribavirin 1000–1200 mg	180 µg + ribavirin 800 mg		3 MIU + ribavirin 1000–1200 mg	180 µg + ribavirin 800 mg	180 µg + ribavirin 1000–1200 mg
	48 weeks	48 weeks	24 weeks	48 weeks	24 weeks	48 weeks	48 weeks	48 weeks	72 weeks
	N=448	N=827	N=207	N=887	N=212	N=210	N=443	N=288	N=156
	%	%	%	%	%	%	%	%	%
Infections and infestations Pharyngitis	<1	-	<1	1	9	10	<1	-	<1
Metabolism and nutrition Anorexia Weight loss	13 4	16 5	20 2	27 7	16 7	13 9	26 10	23 16	15 9

	Hepatitis B	**Hepatitis C**							
	Studies*, ** WV16240 + WV16241	Studies NV15801 + NV15489 + NV15495 + NV15496 + NV15497 **HCV**	Study NV15942 **HCV**	Studies NV15801 + NV15942 **HCV**	Study NR16071 **HCV/n-ALT**		Study NV15801 **HCV**	Study NR15961 **HCV/HIV**	Study MV17150 **HCV peginterferon alfa-2b non-responders:**
Body system	Peginter-feron alfa-2a 180 µg 48 weeks N=448	Peginter-feron alfa-2a 180 µg 48 weeks N=827	Peginter-feron alfa-2a 180 µg + ribavirin 800 mg 24 weeks N=207	Peginter-feron alfa-2a 180 µg + ribavirin 1000–1200 mg 48 weeks N=887	Peginterferon alfa-2a 180 µg + ribavirin 800 mg 24 weeks N=212	48 weeks N=210	IFN alfa-2b 3 MIU + ribavirin 1000–1200 mg 48 weeks N=443	Peginter-feron alfa-2a 180 µg + ribavirin 800 mg 48 weeks N=288	Peginterferon alfa-2a 180 µg + ribavirin 1000–1200 mg 72 weeks N=156
	%	%	%	%	%	%	%	%	%
Psychiatric disorders and nervous system									
Headache	23	52	48	47	44	56	49	35	32
Insomnia	6	20	30	32	35	36	37	19	29
Irritability	3	17	28	24	27	26	27	15	17
Depression	4***	18	17	21	26	27	28	22	16
Dizziness (excluding vertigo)	6	14	13	15	8	17	14	7	10
Impaired concentration	2	9	8	10	9	5	13	2	5
Anxiety	3	6	8	8	10	8	12	8	6
Respiratory organs									
Breathlessness	1	5	11	13	14	15	14	7	11
Cough	2	4	8	13	14	19	7	3	17
Gastrointestinal disorders									
Nausea and vomiting	2	5	8	7	12	13	6	8	6
Nausea	6	24	29	28	32	40	28	24	24
Diarrhea	6	16	15	14	19	26	10	16	13
Abdominal pain	4	15	9	10	9	12	9	7	9
Dyspepsia	2	1	2	6	9	10	5	4	5
Skin									
Hair loss	17	22	25	24	20	28	33	10	18
Pruritus	6	12	25	21	16	20	18	5	22
Dermatitis	<1	9	15	16	<1	2	13	1	1
Dry skin	1	5	13	12	11	9	13	4	17
Rash	4	6	7	9	14	16	5	1	8
Musculoskeletal system									
Muscle pain	25	37	42	38	38	44	49	32	22
Joint pain	10	26	20	22	32	30	23	16	15
General									
Fatigue	21	49	45	49	51	51	53	40	36
Fever	52	35	37	39	30	43	54	41	20
Rigors	6	30	30	25	24	25	34	16	12
Administration site reactions	7	22	28	21	16	16	15	10	12
Weakness	11	7	18	15	22	23	16	26	30
Pain	1	11	9	10	4	3	9	6	6

* In clinical trials a total of 450 patients also received Pegasys in combination with lamivudine (data not shown). The addition of lamivudine had no effect on the safety profile of Pegasys, but also brought no advantage for Pegasys efficacy.

** Studies mainly in Asians

*** 10% in the Caucasian subgroup, 2% in Asians

Frequently reported undesirable effects (≥2% but <10% of patients) on Pegasys/ribavirin combination in hepatitis C or Pegasys monotherapy in hepatitis B or C (HCV and HCV/HIV) were:

Blood and lymphatic system disorders

Lymphadenopathy, anemia, thrombocytopenia

Endocrine disorders

Hypothyroidism, hyperthyroidism

Psychiatric and nervous system disorders

Memory impairment, taste changes, paresthesia, hypesthesia, tremor, emotional disorders, mood swings, nervousness, aggression, decreased libido, impotence, migraine, somnolence, hyperesthesia, nightmares, syncope, suicide attempt, psychosis and hallucination

Eye disorders

Blurred vision, dry eyes (xerophthalmia), eye inflammation, eye pain (see *Warnings and precautions*)

Ear and labyrinth disorders

Vertigo, earache

Cardiac disorders

Palpitations, peripheral edema, tachycardia

Respiratory, thoracic and mediastinal disorders

Upper respiratory tract infection, sore throat, rhinitis, nasopharyngitis, sinus congestion, pulmonary congestion, chest tightness, exertional dyspnea, epistaxis, oral candidiasis, bronchitis

Gastrointestinal disturbances

Gastritis, flatulence, dry mouth, mouth ulceration, gingival bleeding, gingivitis, cheilitis, constipation, stomatitis, dysphagia, glossitis

Skin and subcutaneous tissue disorders

Skin disorders, rash, eczema, psoriasis, urticaria, photosensitivity reactions, increased sweating, night sweats, “flush syndrome”

Musculoskeletal and connective tissue disorders

Bone pain, back pain, neck pain, muscle cramps, muscle weakness, pain in skeletal muscles, arthritis

General disorders and administration site reactions

Flu-like illness, malaise, lethargy, chills, hot flushes, *Herpes simplex*, chest pain

As with other interferons, the following undesirable effects were observed rarely or in occasional to isolated cases during clinical studies with Pegasys/ribavirin combination

therapy or Pegasys monotherapy: lower respiratory tract infection, skin infection, thrombotic thrombocytopenic purpura, autoimmune phenomena (e.g. idiopathic thrombocytopenic purpura, thyroiditis, psoriasis, rheumatoid arthritis, SLE), suicide attempt, psychosis and hallucinations, peripheral neuropathy, retinopathy, optic neuropathy, loss of vision, otitis externa, endocarditis, arrhythmia, atrial fibrillation, pericarditis, angina, cerebral hemorrhage, interstitial pneumonitis with fatal outcome, pulmonary embolism, peptic ulcer, gastrointestinal bleeding, pancreatitis, hepatic dysfunction, fatty liver, cholangitis, liver cancer, corneal ulcer, myositis, sarcoidosis, coma, necrosis at the injection site and overdose of the product.

Tolerability of Pegasys and the undesirable effects observed in patients with renal impairment after a single subcutaneous injection of Pegasys were comparable to those in healthy subjects, and occurred with only slightly greater frequency. The undesirable effects and abnormal laboratory results recorded during the study conformed to the expected findings after interferon therapy.

The following adverse reactions were observed in ≥1% to £2% of HCV/HIV-coinfected patients treated with the combination of Pegasys and ribavirin: hyperlactatemia/lactic acidosis, influenza, pneumonia, affect lability, apathy, tinnitus, pharyngolaryngeal pain, cheilitis, acquired lipodystrophy and chromaturia.

Laboratory values

As with other interferons, abnormal laboratory values were also measured during treatment with Pegasys, namely elevated ALT, electrolyte disturbances (hypokalemia, hypocalcemia, hypophosphatemia), hyperglycemia, hypoglycemia and elevated triglyceride levels (see *Warnings and precautions*).

Elevated ALT values leading to dose modification or discontinuation of treatment were found in 2% (11/887) of the patients treated for 48 weeks with Pegasys 180 µg and ribavirin 1000/1200 mg and in 1.7% (14/827) of the patients given Pegasys monotherapy.

As with other interferons, depressed hematological parameters were observed during treatment with Pegasys. In most cases it was possible to achieve improvement by dose adjustment or a return to pretreatment levels within 4 to 8 weeks of stopping treatment (see *Warnings and precautions*).

Most cases of neutropenia and thrombocytopenia due to treatment with Pegasys in combination with ribavirin or as monotherapy at the recommended dosage were mild (absolute neutrophil count 1.99–0.75 × 10^9/l and platelet count 99–50 × 10^9/l). Moderate (absolute neutrophil count 0.749–0.5 × 10^9/l) and severe (absolute neutrophil count <0.5 × 10^9/l) neutropenia was observed, respectively, in 24% (216/887) and 5% (41/887) of patients treated for 48 weeks with Pegasys 180 µg and ribavirin 1000/1200 mg.

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

An increase in uric acid and indirect bilirubin values associated with hemolysis was observed in some patients treated with peginterferon alfa in combination with ribavirin.

Values returned to baseline levels within 4 weeks after the end of therapy. Only in rare cases (2/755) was this associated with clinical symptoms (acute gout).

In rare cases an association with pancytopenia may be observed on use of alfa interferon, including Pegasys, in combination with ribavirin, and very rarely aplastic anemia has been reported.

Anti-interferon antibodies

Neutralising anti-interferon antibodies occurred in 1–5% of hepatitis C patients treated with Pegasys. Among patients with chronic hepatitis B participating in a phase II study (NV16037), 13% (6/46) developed neutralising anti-interferon antibodies; all were receiving 180 µg of Pegasys. However, the presence of neutralising antibodies did not affect the efficacy or safety of the drug in the treated diseases.

Thyroid function

Treatment with Pegasys was associated with clinically significant changes in thyroid function tests that necessitated clinical intervention (see *Warnings and precautions*). The frequency rates of 4.9% observed with the Pegasys/ribavirin combination (study NV15801) resembled those of other interferons.

Laboratory values in HCV/HIV-coinfected patients

Although hematological undesirable effects such as neutropenia, thrombocytopenia and anemia occurred more frequently in HCV/HIV-coinfected patients, the majority could be managed by dose modification and the use of growth factors. Premature discontinuation of treatment was only rarely necessary. Decrease in ANC below 500 cells/mm^3 was observed in 13% and 11% of patients receiving Pegasys monotherapy and combination therapy, respectively. Decrease in platelets below 50,000/mm^3 was observed in 10% and 8% of patients receiving Pegasys monotherapy and combination therapy, respectively. Anemia (hemoglobin <10 g/dl) was reported in 7% and 14% of patients treated with Pegasys alone or combination therapy, respectively.

When Pegasys is used in combination with other direct-acting anti-HCV agents (DAAs), please see the complete prescribing information for the DAAs concerned.

Post-marketing experience

Since its introduction, very rare cases of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythroblastopenia (pure red cell aplasia [PRCA]) and aggressive behaviour sometimes directed at others (homicidal ideation) have been reported on combination therapy with Pegasys and ribavirin.

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

As in monotherapy, serous retinal detachment has also been reported for combination therapy with Pegasys and ribavirin.

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

OVERDOSAGE

There have been reports of Pegasys overdosage after at least two injections on two consecutive days (instead of one week apart), up to daily injection for one week (i.e. 1260 µg/week). None of these patients manifested unusual or serious events that necessitated discontinuation of treatment. In clinical studies weekly doses of up to 540 and 630 µg were administered, respectively, to patients with renal cell carcinoma and chronic myeloid leukemia. The dose-limiting toxic reactions of fatigue, elevated liver enzymes, neutropenia and thrombocytopenia are typical effects of interferon therapy.

PROPERTIES AND EFFECTS

ATC code: L03AB11

Mechanism of action

Interferons bind to specific interferon alfa-receptors on the cell surface, initiating complex intracellular signal transduction and inducing activation of gene transcription. This influences various biological processes, such as inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation.

Like non-PEG-conjugated alfa interferon, Pegasys displays antiviral and antiproliferative activity *in vitro*.

Pharmacodynamics

While the pharmacodynamic properties of Pegasys are similar to those of natural or non-PEG-conjugated human alfa interferons, its pharmacokinetic properties are fundamentally different. The structure of the 40,000-dalton PEG fraction has a direct effect on the clinical pharmacology because the size and branching of the PEG component determine the absorption, distribution and elimination characteristics.

In healthy subjects a single subcutaneous injection of Pegasys was followed after some 3 to 6 hours by a rise in the serum activity of 2',5'-oligoadenylate synthetase (2',5'-OAS), a marker of antiviral activity. The 2',5'-OAS serum activity induced by peginterferon alfa-2a persisted for more than a week and was higher than the values after single subcutaneous injections of 3 or 18 MIU of interferon. The magnitude and duration of 2',5'-OAS activity after a single subcutaneous injection of 180 µg of Pegasys in patients over 62 years of age were approximately 25% lower than in young healthy subjects.

The 2',5'-OAS response after a single subcutaneous injection of 90 µg of Pegasys was weaker in patients with markedly impaired renal function (creatinine clearance 20 to 40 ml/min) than in those with a clearance of 40 to over 100 ml/min, despite similar drug exposure (AUC and C_{max}) in the two groups (see *Warnings and precautions* and *Pharmacokinetics*).

Treatment with 180 µg of Pegasys in patients with chronic hepatitis C is followed by a biphasic decrease in HCV RNA titre. The first phase begins 24 to 36 hours after the initial dose in patients showing a sustained response, as well as in some patients with no sustained virological response. A second phase occurs within the next 4 to 16 weeks.

Treatment with 180 µg of Pegasys increases virus elimination and improves the virological treatment response compared with conventional alfa interferons.

Clinical efficacy

Chronic hepatitis B

In studies of both HBeAg-positive (WV16240) and HBeAg-negative hepatitis B (WV16241), Pegasys at a dosage of 180 µg once weekly achieved significantly better sustained virological response rates than lamivudine.

Clinical trial results

Both clinical trials recruited patients with chronic hepatitis B who had active viral replication demonstrated by HBV DNA, elevated levels of ALT and liver biopsy-proven 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 + placebo with Pegasys + lamivudine or lamivudine alone. No HBV/HIV-coinfected patients were included in these trials.

Response rates at the end of follow-up for the two studies are presented in Table 6. HBV DNA was measured by the Cobas Amplicor™ HBV Monitor Assay (limit of detection 200 copies/ml).

Table 6 Serological, virological and biochemical response rates in chronic hepatitis B

	HBeAg-positive patients **Study WV16240**			**HBeAg-negative/anti-HBe-positive patients** **Study WV16241**		
	Pegasys 180 µg + **placebo** (N=271)	**Pegasys** 180 µg + **lamivudine** 100 mg (N=271)	**Lamivudine** 100 mg (N=272)	**Pegasys** 180 µg + **placebo** (N=177)	**Pegasys** 180 µg + **lamivudine** 100 mg (N=179)	**Lamivudine** 100 mg (N=181)
HBeAg seroconversion	32% [1]	27%	19%	Not applicable	Not applicable	Not applicable
HBV DNA* (no longer detectable)	32% [2]	34%	22%	43% [5]	44%	29%
ALT normalisation	41% [3]	39%	28%	59% [6]	60%	44%

HBsAg seroconversion	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

All patients who completed the phase III studies were eligible for entry into a long-term follow-up study (WV16866). Among patients from study WV16240 who received Pegasys monotherapy and entered the long-term follow-up study, the rate of sustained HBeAg seroconversion 12 months after the end of therapy was 48% (73/153). In patients receiving Pegasys monotherapy in study WV16241, the rates of HBV DNA response and ALT normalisation 12 months after end of treatment were 42% (41/97) and 59% (58/99), respectively.

Another study (NEPTUNE, WV19432) evaluated the efficacy and safety of Pegasys administered for 24 or 48 weeks at doses of 90 µg or 180 µg in HBeAg-positive patients. The study was a multicentre, double-blind, randomised non-inferiority trial with a factorial design. Five hundred and fifty-one patients were randomised to one of four treatment groups: 90 µg for 24 weeks (n=141); 180 µg for 24 weeks (n=136); 90 µg for 48 weeks (n=138); 180 µg for 48 weeks (n=136).

Table 7 below summarises the response rates by treatment group at 24 weeks post treatment in the per protocol population.

Table 7 Summary of efficacy results – per protocol population, response rates at 24 weeks after completion of study treatment

	Treatment group			
	90 µg once weekly for 24 weeks	180 µg once weekly for 24 weeks	90 µg once weekly for 48 weeks	180 µg once weekly for 48 weeks
	N=142	N=140	N=132	N=130
Primary endpoint – response rates, N (%)				
HBeAg seroconversion (24 weeks post treatment)	20 (14.08%)	32 (22.86%)	34 (25.76%)	47 (36.15%)
Secondary endpoints – response rates, N (%)				
HBeAg loss	21 (14.79%)	32 (22.86%)	35 (26.52%)	47 (36.15%)
HBsAg seroconversion	0 (0.00%)	0 (0.00%)	2 (1.52%)	3 (2.31%)
HBsAg loss	1 (0.70%)	0 (0.00%)	3 (2.27%)	3 (2.31%)
ALT normalisation	43 (30.28%)	43 (30.71%)	57 (43.18%)	68 (52.31%)
HBV DNA suppression (<20,000 IU/ml)	31 (21.83%)	30 (21.43%)	43 (32.58%)	55 (42.31%)
HBV DNA suppression (<2,000 IU/ml)	16 (11.27%)	16 (11.43%)	30 (22.73%)	39 (30.00%)

To summarise, 24-week treatment was inferior to 48-week treatment with respect to the primary endpoint, HBeAg seroconversion at 24 weeks post treatment (OR 48/24 weeks = 2.17, 95% CI = 1.43–3.31, p-value (for non-inferiority) = 0.749) and a dose of 90 µg was inferior to a dose of 180 µg (OR 180 µg/90 µg = 1.79, 95% CI = 1.18–2.72, p-value (for non-inferiority) = 0.410). As regards the secondary endpoints investigated in the study, the general trends were consistent with the primary endpoint; the highest response rates were consistently achieved in the group treated with 180 µg for 48 weeks. Patients who received 180 µg Pegasys for 48 weeks showed an increased incidence of adverse events. These events were not serious, however.

Study ML18253 assessed the effects of extended treatment (i.e. longer than 48 weeks) in HBeAg-negative patients. Out of a planned sample size of 250 patients, a total of 131 patients, primarily with genotype D, were randomised to treatment with 180 µg Pegasys for 48 weeks (n=52), 180 µg Pegasys for 48 weeks + 135 µg for an additional 48 weeks (n=53) or 180 µg Pegasys + 100 mg/day lamivudine for 48 weeks followed by 135 µg Pegasys for an additional 48 weeks (n=26).

Table 8 below summarises the response rates by treatment group at 48 weeks post treatment in the ITT population.

Table 8 Summary of efficacy results – intent-to-treat population, Study ML18253, response rates 48 weeks after completion of study treatment

	Group A: PEG-IFN 180 µg/week 48 weeks (N=51)	**Group B: PEG-IFN 180 µg/week 48 weeks + PEG-IFN 135 µg/week for a further 48 weeks (N=52)**	**Group C: PEG-IFN 180 µg/week + LAM 100 mg /once daily 48 weeks + PEG-IFN 135 µg/week for a further 48 weeks (N=25)**	**Comparison Group A versus Group B[†]**
Primary endpoint – response rates, N (%)				
Combined response: ALT normalisation and HBV DNA <3,400 IU/ml	6 (11.8%)	13 (25.0%)	5 (20.0%)	P = 0.08
Secondary endpoints – response rates, N (%)				

	Group A: PEG-IFN 180 µg/week 48 weeks (N=51)	**Group B: PEG-IFN 180 µg/week 48 weeks + PEG-IFN 135 µg/week for a further 48 weeks (N=52)**	**Group C: PEG-IFN 180 µg/week + LAM 100 mg /once daily 48 weeks + PEG-IFN 135 µg/week for a further 48 weeks (N=25)**	**Comparison Group A versus Group B†**
ALT normalisation	18 (35.3%)	18 (34.6%)	9 (36.0%)	P = 0.94
Virological response				
HBV DNA < 3,400 IU/ml:	6 (11.8%)	16 (30.8%)	5 (20.0%)	P = 0.02
HBV DNA < 2,000 IU/ml:	6 (11.8%)	15 (28.8%)	5 (20.0%)	P = 0.03
HBV DNA < limit of detection:	1 (2.0%)	4 (7.7%)	2 (8.0%)	P = 0.18
HBsAg loss and anti-HBs seroconversion	0 (0.0%)	4 (7.7%)	0 (0.0%)	P = 0.04
Histological response	7 (13.7%)	3 (5.8%)	2 (8.0%)	P = 0.17

†=Chi square test for independence

Only limited conclusions could be drawn from this study because of the small sample size. With respect to comparative safety, extending treatment with Pegasys to 96 weeks (with a dose reduction at the end of 48 weeks) did not adversely impact tolerability compared with treatment for 48 weeks and was not associated with an increase in serious clinical events.

Chronic hepatitis C

Results of clinical trials in treatment-naïve patients

Pegasys combination therapy in patients with elevated transaminases

In two studies (NV15801 and NV15942) a total of 2405 patients were treated.

¨ In study NV15801, 1149 patients were randomised and 1121 treated. The number of patients not treated was similar in both combination arms (12/465 on Pegasys + ribavirin, 13/457 on interferon alfa-2b + ribavirin). A total of 1121 patients were treated for a year with one of the following combinations:

- Pegasys (180 µg once weekly) + placebo, N=224
- Pegasys (180 µg once weekly) + ribavirin (1000/1200 mg/day), N=453
- Interferon alfa-2b (3 MIU thrice weekly) + ribavirin (1000/1200 mg/day), N=444

In this trial the combination of Pegasys and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin or Pegasys monotherapy (see Table 9). Significantly increased efficacy compared with interferon alfa-2b and ribavirin was observed in patients with genotype 1 or genotype 2/3 infection and in patients with cirrhosis (see Table 9). The sustained virological response in cirrhotic patients treated with the combination of Pegasys and ribavirin was 43%. Sustained virological response was determined 24 weeks after the end of treatment.

Table 9 Sustained virological response in study NV15801 in hepatitis C patients (N=number of treated patients)

Sustained response	**PEG-IFN alfa-2a** N=224	**PEG-IFN alfa-2a ribavirin** N=453	**IFN alfa-2b ribavirin** N=444
Overall	29%	54%	45%
Genotype 1	20%	45%	36%
Genotype non-1	46%	72%	60%

Virological response was defined as HCV RNA below the detection limit as measured by the Cobas Amplicor™ HCV Test, version 2.0 (detection limit 100 copies/ml equivalent to 50 IU/ml).

¨ In study NV15942 a total of 1284 patients were treated for 24 or 48 weeks with one of the following combinations:

- Pegasys (180 µg once weekly) + ribavirin (800 mg/day) for 24 weeks, N=207
- Pegasys (180 µg once weekly) + ribavirin (1000/1200 mg/day, depending on body weight) for 24 weeks, N=280
- Pegasys (180 µg once weekly) + ribavirin (800 mg/day) for 48 weeks, N=361
- Pegasys (180 µg once weekly) + ribavirin (1000/1200 mg/day, depending on body weight) for 48 weeks, N=436

An overview of virological response rates from study NV15942 is shown in Table 10.

Table 10 Sustained virological response in study NV15942 in hepatitis C patients

	Pegasys combination therapy **Non-cirrhotic and cirrhotic patients*** **Study NV15942**	
	Pegasys 180 µg + **ribavirin** 1000/1200 mg (N=436) 48 weeks	
Sustained response for all genotypes	63%**	59%***

* 75% of treated patients were non-cirrhotic, 18% showed borderline cirrhosis and 7% were cirrhotic.

** Virological response was defined as HCV RNA below the detection limit between weeks 12 and 24 after the end of treatment. The HCV RNA test used was the Cobas Amplicor™ HCV Test, version 2.0 (detection limit 100 copies/ml equivalent to 50 IU/ml).

*** Virological response was defined as HCV RNA below the detection limit in two consecutive assays performed after the end of treatment at an interval of 21 days from each other. The HCV RNA test used was the Cobas Amplicor™ HCV Test, version 2.0 (detection limit 100 copies/ml equivalent to 50 IU/ml).

Virological response in patients treated with Pegasys + ribavirin is shown as a function of genotype and viral load in Table 11. The results of study NV15942 provide the foundation for a dosing recommendation based on genotypes (see Table 11).

These response patterns were not influenced by viral load or the presence or absence of cirrhosis. The treatment recommendations are therefore independent of these baseline conditions.

Table 11 Sustained virological response as a function of genotype and viral load – Pegasys combination therapy with ribavirin

	Study NV15942*			
	Pegasys 180 µg + **ribavirin** 800 mg 24 weeks	**Pegasys** 180 µg + **ribavirin** 1000/1200 mg 24 weeks	**Pegasys** 180 µg + **ribavirin** 800 mg 48 weeks	**Pegasys** 180 µg + **ribavirin** 1000/1200 mg 48 weeks
Genotype 1	29% (29/101)	42% (49/118)	41% (102/250)	52% (142/271)
Low viral load	41% (21/51)	52% (37/71)	55% (33/60)	65% (55/85)
High viral load	16% (8/50)	26% (12/47)	36% (69/190)	47% (87/186)

Genotype 2/3	84% (81/96)	81% (117/144)	79% (78/99)	80% (123/153)
Low viral load	85% (29/34)	83% (39/47)	88% (29/33)	77% (37/48)
High viral load	84% (52/62)	80% (78/97)	74% (49/66)	82% (86/105)
Genotype 4	0% (0/5)	67% (8/12)	63% (5/8)	82% (9/11)

* Virological response was defined as HCV RNA below the detection limit between weeks 12 and 24 after the end of treatment. The HCV RNA test used was the Cobas Amplicor™ HCV Test, version 2.0 (detection limit 100 copies/ml equivalent to 50 IU/ml).

In all trials (including Pegasys monotherapy; see below), most patients treated with Pegasys showed normalisation or reduction of serum ALT during treatment. It is possible, however, that normal ALT levels may not be restored before treatment with Pegasys has ended, even in patients in whom HCV RNA has fallen below the detection limit. Regardless of ALT normalisation, virological analysis is a more reliable instrument for determining the efficacy of Pegasys therapy.

Pegasys combination therapy in patients with normal transaminases

HCV-infected patients with normal ALT levels (see Table 12)

In study NR16071, HCV-infected patients with normal ALT levels were randomised to 24 or 48 weeks of treatment with Pegasys (180 µg/week) and ribavirin (800 mg/day), followed by a treatment-free follow-up or no treatment for 72 weeks. The SVR values reported in the treatment groups of this trial were similar to those in the corresponding treatment groups of study NV15942.

In study NR16071 the sustained virological response rate in patients treated for 48 weeks was significantly higher (52%) than in patients treated for 24 weeks (30%) ($p<0.001$). Sustained virological response in both active treatment groups was also significantly higher than in the untreated control group ($p<0.001$). No patient from the untreated control group achieved a sustained virological response.

Patients infected with HCV genotype 1 had significantly higher SVR rates after a 48-week treatment (40%) than after 24 weeks of treatment (13%) (odds ratio 4.47, 95% confidence interval 2.47–8.08, $p<0.001$). In patients infected with genotype 2/3 virus, the sustained virological response rate showed no significant difference between the 24-week (72%) and 48-week treatment (78%) (odds ratio 1.40, 95% confidence interval 0.59–3.30, $p=0.452$).

Table 12 Sustained virological response as a function of genotype

	Study NR16071		
	Pegasys 180 µg + **ribavirin** 800 mg 24 weeks	**Pegasys** 180 µg + **ribavirin** 800 mg 48 weeks	**No treatment**

Genotype 1*	13% (19/144)	40% (57/141)	0%
Genotype 2/3	72% (42/58)	78% (46/59)	0%

* Study NR16071 was conducted with a ribavirin dose differing from the 1000/1200 mg/day recommended for genotype 1 (see *Dosage and administration*).

Predictability of response

Patients demonstrating an early virological response by week 12 have an increased probability of achieving a sustained virological response with a full course of therapy. An early virological response is defined as HCV RNA below the detection limit or at least a 99% reduction in viral titre from baseline by week 12 of therapy.

Pooling of data from the groups common to studies NV15801 and NV15942 results in a negative predictive value of 95% for combination therapy with Pegasys. Calculation from the pooled data from the two groups common to studies NV15801 and NV15942 gave a value of 66% for the positive predictive value of virological response after 12 weeks. Of the 776 patients who had responded by week 12 of treatment, 514 achieved a sustained virological response.

The possibility of 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 13).

Table 13 Sustained virological response in patients infected with HCV genotype 1 or 4 after rapid virological response within 4 weeks to combined therapy with Pegasys and ribavirin

Study NV15942		
	Pegasys 180 µg + **ribavirin 1000/1200 mg** 24 weeks	**Pegasys 180 µg** + **ribavirin 1000/1200 mg** 48 weeks
Genotype 1 with 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 without 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 with RVR	(5/6)	(5/5)
Genotype 4 without	(3/6)	(4/6)

RVR		

Low viral load = ≤800,000 IU/ml; high viral load = >800,000 IU/ml
RVR = rapid virological 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 infection was examined in study NV17317. The criterion was sustained virological response after rapid virological response within 4 weeks (see Table 14).

In study NV17317 in patients infected with viral genotype 2 or 3, all patients received 180 µg peginterferon alfa-2a subcutaneously once weekly and 800 mg ribavirin, and were randomised to treatment for either 16 or 24 weeks. Overall, the 16- and 24-week treatments were not equivalent (see Table 14), treatment for 16 weeks resulting in a lower sustained virological response rate (65%) than treatment for 24 weeks (76%). However, retrospective analysis of patients with a low baseline viral load who were HCV RNA-negative at week 4 showed similar sustained virological response rates – 89% and 94% – after 16 and 24 weeks of treatment (see Table 14).

Table 14 Sustained virological response in patients infected with HCV genotype 2 or 3 after rapid virological response within 4 weeks to combined therapy with Pegasys and ribavirin

Study NV17317		
	Pegasys 180 µg + ribavirin 800 mg 16 weeks	**Pegasys 180 µg + ribavirin 800 mg** 24 weeks
Genotype 2 or 3	65% (443/679)	76% (478/630)
Genotype 2 or 3 with 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 without 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 virological response, HCV RNA-negative within 4 weeks

A higher relapse rate must be expected with the 16-week treatment, so that treatment duration should be determined on a case-by-case basis, depending on the clinical situation and taking relevant risk factors into account. Preference should be given to the 24-week treatment, if well tolerated (see Table 15).

Table 15 Relapse after virological response after the end of treatment in genotype 2 or 3 patients with a rapid virological response

Study NV17317			
	Peginterferon alfa-2a 180 µg + ribavirin 800 mg 16 weeks	**Peginterferon alfa-2a 180 µg + ribavirin 800 mg** 24 weeks	**Treatment difference (95% confidence interval)**
Genotype 2 or 3 rapid virological response	15% (67/439)	6% (23/386)	9.3% (5.2%; 13.6%)
Low viral load	6% (10/155)	1% (2/141)	5% (0.6%; 10.3%)
High viral load	20% (57/284)	9% (21/245)	11.5% (5.6%; 17.4%)

Chronic hepatitis C prior treatment non-responder patients

In study MV17150, patients who were non-responders to previous therapy with pegylated interferon alfa-2b (i.e. failing to achieve undetectable HCV RNA) were randomised to four different treatments:

Pegasys 360 µg/week for 12 weeks, followed by 180 µg/week for a further 60 weeks

Pegasys 360 µg/week for 12 weeks, followed by 180 µg/week for a further 36 weeks

Pegasys 180 µg/week for 72 weeks

Pegasys 180 µg/week for 48 weeks

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

The mean interval between the previous and renewed treatments in the four treatment groups ranged from 504 to 592 days.

Multiple regression and pooled group analyses evaluating the influence of treatment duration and use of induction dosing clearly identified treatment duration for 72 weeks as the primary driver for achieving a sustained virological response. Differences in sustained virological response (SVR) based on treatment duration, demographics and best responses to previous treatment are displayed in Table 16.

Table 16 Week 12 virological response (VR) and sustained virological response (SVR) in patients with virological response at week 12 after treatment with Pegasys and ribavirin combination therapy in non-responders to peginterferon alfa-2b + ribavirin

	Pegasys 360/180 or 180 µg + **ribavirin** 1000/1200 mg 72 or 48 weeks (N=942) **Patients with VR at week 12[a] (N=876)**	**Pegasys** 360/180 or 180 µg + **ribavirin** 1000/1200 mg 72 weeks (N=473) **SVR in patients with VR at week 12[b] (N=100)**	**Pegasys** 360/180 or 180 µg + **ribavirin** 1000/1200 mg 48 weeks (N=469) **SVR in patients with VR at week 12[b] (N=57)**
Overall	18% (157/876)	57% (57/100)	35% (20/57)
Low viral load	35% (56/159)	63% (22/35)	38% (8/21)
High viral load	14% (97/686)	54% (34/63)	32% (11/34)
Genotype 1/4	17% (140/846)	55% (52/94)	35% (16/46)
Low viral load	35% (54/154)	63% (22/35)	37% (7/19)
High viral load	13% (84/663)	52% (30/58)	35% (9/26)
Genotype 2/3	58% (15/26)	(4/5)	(3/10)
Low viral load	(2/5)	—	(1/2)
High viral load	(11/19)	(3/4)	(1/7)
Cirrhosis status			
Cirrhosis	8% (19/239)	(6/13)	(3/6)
No cirrhosis	22% (137/633)	59% (51/87)	34% (17/50)
Best response during previous treatment			
$\geq 2\log_{10}$ decline in HCV RNA	28% (34/121)	68% (15/22)	(6/12)
$<2\log_{10}$ decline in HCV RNA	12% (39/323)	64% (16/25)	(5/14)
No best previous response	19% (84/432)	49% (26/53)	29% (9/31)

High viral load = >800,000 IU/ml; low viral load = ≤800,000 IU/ml

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

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

In the HALT-C study, patients with chronic hepatitis C and advanced fibrosis or cirrhosis who were non-responders to previous treatment with interferon alfa or pegylated interferon alfa monotherapy or in combination with ribavirin received Pegasys 180 µg/week and ribavirin 1000/1200 mg daily. Patients who achieved undetectable levels of HCV RNA after 20 weeks of treatment remained on Pegasys + ribavirin combination therapy for a total of 48 weeks and were then followed for 24 weeks after the end of treatment. Sustained virological response was dependent on the previous treatment regimen. Treatment outcome was poorest among patients who were non-responders to pegylated interferon in combination with ribavirin. This was the most difficult-to-treat subpopulation of non-responders, and their result was similar to the rate of sustained virological response observed in the 48-week treatment arms of study MV17150. Despite higher sustained virological response rates in non-responders to interferon or pegylated interferon monotherapy, efficacy in these less difficult-to-treat non-responders remains substantially lower than that achievable in treatment-naïve patients (see Table 17).

Table 17 Sustained virological response in relation to treatment duration and non-responder population

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

* HALT-C data
** MV17150 data

When Pegasys is used in combination with other direct-acting anti-HCV agents (DAAs), please see the complete prescribing information for the DAAs concerned.

Pegasys monotherapy

The efficacy of Pegasys was demonstrated in three double-blind, randomised clinical studies. A total of 1130 previously untreated patients with chronic hepatitis C were treated for 48 weeks. Twenty-four weeks after the end of treatment, viral titres were determined and the patients subjected to liver biopsy.

Sustained inhibition of viral replication occurred in 34% (28–39%) of patients treated with Pegasys 180 µg, as compared with only 15% (11–19%) of patients treated with interferon alfa-2a (Roferon-A) 3 MIU/6 MIU. In patients with advanced fibrosis or cirrhosis, sustained viral inhibition occurred in 29% of those treated with Pegasys, as compared with only 6% of patients treated with interferon alfa-2a.

Comparing the changes in liver histology in patients without cirrhosis, 58 to 63% (depending on the study) of patients treated with Pegasys showed an improvement, as documented by a decrease of more than two points in the Knodell histology activity index. This occurred in only 45% of cases with interferon alfa-2a. Among patients with cirrhosis, 54% of those receiving Pegasys showed improved liver histology, as against only 31% of patients treated with interferon alfa-2a.

Superior efficacy of Pegasys compared to interferon alfa-2a was also demonstrated in terms of histological response, including in patients without sustained virological response and patients with cirrhosis and/or HCV/HIV coinfection.

The undesirable-effect and safety profile of Pegasys in patients without cirrhosis is similar to that of Roferon-A (interferon alfa-2a). Among cirrhotic patients, thrombocytopenia, dose reduction and discontinuation of treatment were more frequent with Pegasys, and four patients in the study of CHC with cirrhosis died while or after taking Pegasys (4/183): one on 90 µg (1/96) after liver failure on day 456, and three on 180 µg (3/87 = 3.4%). Of the latter three patients, one died on day 397 following hematemesis, melena and liver failure, one on day 549 of metastatic adenocarcinoma, and one on day 81 as a result of cerebral hemorrhage, probably caused by thrombocytopenia. While an association with Pegasys was assumed only for the cerebral hemorrhage, the association between Pegasys and liver failure in two patients cannot be excluded.

HCV/HIV-coinfected patients

In study NR15961, 860 HCV/HIV-coinfected patients were randomised and treated with Pegasys 180 µg/week + placebo, Pegasys 180 µg/week + ribavirin 800 mg/day or interferon alfa-2a 3 MIU three times weekly + ribavirin 800 mg/day for 48 weeks followed by a 24-week treatment-free follow-up. The combination of Pegasys with ribavirin induced an overall higher sustained virological response rate (40%) than Pegasys alone (20%) (odds ratio [95% confidence interval] = 2.89 [1.93 to 4.32], p<0.0001 [stratified Cochran-Mantel-Haenszel test]) or than interferon alfa-2a in combination with ribavirin (12%) (odds ratio [95% confidence interval] = 5.40 [3.42 to 8.54], p<0.0001 [stratified Cochran-Mantel-Haenszel test]). In HCV/HIV-coinfected patients with HCV genotype 1 the sustained virological response rate to the combination of Pegasys + ribavirin was 29% (51/176) vs 7% (12/171) in the group with interferon alfa-2a + ribavirin. In HCV/HIV-coinfected patients with HCV genotypes 2 or 3 the sustained virological response rate to the combination of Pegasys + ribavirin was 62% (59/95) vs 20% (18/89) in the group with interferon alfa-2a + ribavirin.

PHARMACOKINETICS

Absorption

Serum concentrations of peginterferon alfa-2a are detectable in healthy subjects within 3 to 6 hours of a single subcutaneous injection of 180 µg of Pegasys, reaching about 80% of their peak level within 24 hours. Peak serum concentrations are measured 72 to 96 hours post-dose (AUC 1743 ± 459 ng·h/ml, C_{max} 14 ± 2.5 ng/ml). The absolute bioavailability of Pegasys is 61 to 84%, depending on the study, and is thus comparable with the value determined for interferon alfa-2a.

Distribution

The steady-state volume of distribution (V_d) after intravenous administration was 6 to 14 litres, indicating that peginterferon alfa-2a is found mainly in the bloodstream and extracellular fluid. Mass balance, tissue distribution and whole-body

autoradioluminographic studies in rats show that in addition to its high concentration in the blood, peginterferon alfa-2a is distributed in the liver, kidney and bone marrow.

Metabolism

The metabolism of Pegasys has not been elucidated. Studies in rats suggest that Pegasys is metabolised in the liver and that the metabolites are mainly excreted via the kidneys.

Elimination

Systemic elimination of Pegasys in healthy volunteers is about 100 times lower than that of endogenous interferon alfa-2a. Intravenously administered Pegasys has a terminal half-life of some 60 to 80 hours, as compared with 3 to 4 hours in the case of interferon alfa. The terminal half-life after subcutaneous administration in patients is longer, with a mean value of 160 hours (84 to 353 hours). The measured terminal half-lives probably reflect not only the elimination phase of Pegasys but also its prolonged absorption phase.

The concentration of Pegasys on once-weekly dosing increases in proportion to dose in both healthy subjects and patients with chronic hepatitis B or C.

In patients with chronic hepatitis B or C the serum level of peginterferon alfa-2a following weekly administration for 6 to 8 weeks is twice to three times that measured after a single dose. No further increase in serum concentration is seen after eight weeks of once-weekly dosing. The peak-to-trough ratio after 48 weeks of treatment is 1.5 to 2. The serum concentration of peginterferon alfa-2a is maintained for one week (168 hours).

Pharmacokinetics in special patient populations

Patients with renal impairment

Pharmacokinetic data obtained in 23 persons with a creatinine clearance ranging from over 100 ml/min (normal renal function) to 20 ml/min (severe renal impairment) showed no evidence of a relevant association between the pharmacokinetic profile of peginterferon alfa-2a and creatinine clearance. The effect of diminished renal function on Pegasys pharmacokinetics is so small that dose adjustment is unnecessary in patients with renal impairment if creatinine clearance exceeds 20 ml/min *(*see *Dosage and administration* and *Warnings and precautions).*

In patients with end-stage renal disease undergoing hemodialysis, Pegasys clearance is reduced by 25–45%, and first administration of a 135 µg dose results in exposure similar to that with a 180 µg dose in patients with normal renal function.

Sex-specific differences

The pharmacokinetic properties of Pegasys after a single subcutaneous injection were similar in healthy male and female subjects.

Elderly patients

After a single subcutaneous injection of 180 µg, delayed but sustained absorption of Pegasys was observed in persons aged over 62 years (t_{max} 115 h in persons over 62 years vs 82 h in young healthy subjects). AUCs were slightly higher in persons over 62 years

(1663 vs 1295 ng·h/ml), while peak concentrations were essentially the same (9.1 vs 10.3 ng/ml).

Based on the availability of the active substance, pharmacodynamic effect and tolerability, a lower dose of Pegasys is not necessary in elderly patients (see *Dosage and administration*).

Non-cirrhotic and cirrhotic patients

The pharmacokinetic behaviour of Pegasys was similar in healthy subjects and patients with hepatitis B or C. The pharmacokinetic profiles and plasma concentrations of peginterferon alfa-2a are comparable in hepatitis C patients without and with cirrhosis (compensated, Child-Pugh A).

No data are available on patients with decompensated liver disease (see *Contraindications*).

Injection site

Subcutaneous administration of Pegasys should be limited to the abdomen and thigh. The availability of Pegasys was decreased in studies with injection into the upper arm compared to injection into the abdomen or thigh (see *Dosage and administration*).

PRECLINICAL DATA

Because of the species specificity of human interferon, Pegasys has been subjected to only limited toxicity testing. The toxicity studies of Pegasys are based on those of interferon alfa-2a.

As with other alfa interferons, administration of Pegasys to female monkeys led to prolongation of the menstrual cycle. A normal menstrual cycle returned once treatment was stopped.

Teratogenesis

Pegasys has not been tested for teratogenicity. Treatment with interferon alfa-2a in rhesus monkeys led to a statistically significant increase in abortive activity.

Although no teratogenic effects were observed in offspring born at term, malformations in humans cannot be excluded.

Pegasys + ribavirin

When used in combination with ribavirin in monkeys, Pegasys caused no effects that had not already been seen with the separate substances. 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.

During combination therapy with ribavirin the prescribing information on ribavirin should also be consulted with regard to preclinical data.

SPECIAL REMARKS

Incompatibilities

As no incompatibility studies have been performed, this medicinal product must not be mixed with other medicinal products.

Notes on handling and disposal

The vial, prefilled syringe and prefilled pen containing Pegasys solution for injection are intended for single use only. Discard any unused solution.

When administering Pegasys parenterally, check for change in colour and the presence of particulate matter before administration, if solution and container permit.

The Pegasys patient information leaflet contains detailed instructions on preparing and administering Pegasys in a prefilled syringe or pen.

Disposal of syringes/sharp or pointed parts of the prefilled syringe

Follow the points below when using and disposing of syringes and other medical sharps:

- Never reuse needles or syringes.
- Dispose of used needles and syringes in a sharps bin (a perforation-proof disposable container).
- Keep the bin out of reach of children.
- Do not dispose of the sharps bin in the household waste.
- When filled, dispose of the sharps bin according to local instructions or the advice of your doctor or pharmacist.

Disposal of syringes/sharp or pointed parts of the prefilled pen

Refer to the instructions below for proper disposal:

- There is no need to put the cap back on.
- Dispose of the used prefilled pen and cap in a perforation-proof disposable container.
- Keep this container out of reach of children.

Home user patients should be provided with a perforation-proof sharps bin for discarding used syringes, prefilled pens and needles.

Do not discard unused or expired medicines.

Whenever possible avoid inappropriately disposing of medicines in the environment. Do not dispose of medicines in either waste water or the household waste.

Stability

The product must not be used after the date marked with EXP on the container.

Special instructions for storage

Store the product away from light in the sealed original package at a temperature of 2–8°C (in refrigerator).

Do not freeze.

PACKS

Vials with 135 µg/ml of solution for injection	1, 4
Vials with 180 µg/ml of solution for injection	1, 4
Prefilled syringes with 135 µg/0.5 ml of solution for injection and injection needle	1, 4
Prefilled syringes with 180 µg/0.5 ml of solution for injection and injection needle	1, 4
Prefilled pen (ProClick™) with 135 mg/0.5 ml of solution for injection	1
Prefilled pen (ProClick™) with 180 mg/0.5 ml of solution for injection	1

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at November 2013

Vials and prefilled syringes:

Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel; manufacturing site Kaiseraugst

Prefilled pens:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Catalent Belgium SA, Brussels, Belgium