PRODUCT MONOGRAPH

PrPEGASYS®

peginterferon alfa-2a injection

Pre-filled syringes: 180 mcg/0.5 mL

Single-use Vials: 180 mcg/1 mL

ProClick® Autoinjector: 180 mcg/0.5 mL

Biological Response Modifier

Professed Standard

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Imported and Distributed by Accelera Pharma Canada Inc.,
Mississauga, ON L5L 5Z9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Information as set forth in this label only applies to PEGASYS.

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Subcutaneous	Solution in vial: 180 mcg/1.0 mL	Benzyl alcohol *For a complete listing see Dosage Forms, Composition and Packaging section.*
Subcutaneous	Solution in pre-filled syringe: 180 mcg/0.5 mL Solution in ProClick® autoinjector: 180 mcg/0.5 mL	Benzyl alcohol *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

PEGASYS: Peginterferon alfa-2a is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20 kD) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40 kD). Interferon alfa-2a is produced biosynthetically using recombinant DNA technology, and is the product of a cloned human leukocyte interferon gene inserted into and expressed in *E. coli*.

INDICATIONS AND CLINICAL USE

Chronic Hepatitis C (CHC)

PEGASYS (peginterferon alfa-2a) is indicated for the treatment of Chronic Hepatitis C in:

- Adult patients without cirrhosis
- Adult patients with compensated cirrhosis,

including HCV/HIV co-infection patients with stable HIV disease with or without antiretroviral therapy.

Chronic Hepatitis B (CHB)

PEGASYS is indicated for the treatment of both HBeAg-positive and HBeAg-negative chronic hepatitis B in:

- Patients with compensated liver disease, liver inflammation and evidence of viral replication (both cirrhotic and non-cirrhotic disease).

Geriatrics (> 65 years of age): Clinical studies of PEGASYS alone or in combination with COPEGUS did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects.

Pediatrics (< 18 years of age): PEGASYS is not authorized for use in children and adolescents under the age of 18 years (see WARNINGS AND PRECAUTIONS: Special Populations, Pediatrics).

CONTRAINDICATIONS

PEGASYS (peginterferon alfa-2a) is contraindicated in:

- Patients with known hypersensitivity to alpha interferons, to *E. coli*-derived products, to polyethyleneglycol or to any component of the product (see DOSAGE FORMS, COMPOSITION AND PACKAGING),
- Patients with autoimmune hepatitis,
- Patients with decompensated cirrhosis,
- HIV-HCV patients with cirrhosis and a base-line Child-Pugh score ≥ 6, except if only the high score (≥ 6) is induced by drugs known to cause indirect hyperbilirubinemia and without evidence of clinical hepatic decomposition (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreas and DOSAGE AND ADMINISTRATION: Special Populations).
- Patients with a history of autoimmune disease.
- Neonates and infants because PEGASYS contains benzyl alcohol. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known.
- Patients who have a pre-existing severe psychiatric condition or a history of a severe psychiatric disorder, who have pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication, and in women who are breast feeding.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Alpha interferons, including PEGASYS (peginterferon alfa-2a), cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many cases, but not all cases, these disorders resolve after stopping interferon therapy (see WARNINGS AND PRECAUTIONS).

General

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

The safety and efficacy of PEGASYS have not been established in patients who have failed other alpha interferon treatments.

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

Patients should be informed regarding the potential benefits and risks attendant to the use of PEGASYS. If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including review of the contents of the Consumer Information, which does not disclose all possible adverse effects of PEGASYS (see PART III: CONSUMER INFORMATION).

If home use is prescribed, patients should be thoroughly instructed in the importance of proper disposal of, and cautioned against, reuse of any needles and syringes.

Patients should be cautioned not to change to other pegylated interferons or switch to other alpha interferons without a medical consultation; changing from one interferon to another may require dosage change or adjustment.

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

Cardiovascular

Cardiovascular events such as hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with interferon therapies, including PEGASYS. Therefore, PEGASYS should be administered with caution to patients with pre existing cardiac disease. Patients should be assessed before initiation of therapy and should be appropriately monitored during therapy. It is recommended that patients who have pre existing cardiac abnormalities have an electrocardiogram prior to initiation of PEGASYS. As

with other alpha interferons, treatment with PEGASYS is not recommended in patients with pre existing severe, unstable or uncontrolled cardiac disease; if there is any deterioration of cardiovascular status, PEGASYS therapy should be suspended or discontinued.

Cerebrovascular

Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with interferon alfa-based therapies, including PEGASYS. Events occurred in patients with few or no reported risk factors for stroke, including patients less than 45 years of age. Because these are spontaneous reports, estimates of frequency cannot be made and a causal relationship between interferon alfa-based therapies and these events is difficult to establish.

Endocrine and Metabolism

Endocrine

As with other interferons, PEGASYS may cause or aggravate hypothyroidism and hyperthyroidism. Hypoglycemia, hyperglycemia, and diabetes mellitus have been observed in patients treated with PEGASYS. Patients with these conditions at baseline who cannot be effectively controlled by medication should not be started on PEGASYS therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue PEGASYS therapy.

Gastrointestinal

Colitis

Hemorrhagic/ischemic colitis, sometimes fatal, has been observed within 12 weeks of starting alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations of colitis. PEGASYS treatment should be discontinued immediately if these symptoms develop. The colitis usually resolves within 1 to 3 weeks following discontinuation of alpha interferon. Ulcerative colitis has also been observed in patients treated with alpha interferon.

Growth and Development (Pediatric Patients)

During the course of PEGASYS plus ribavirin therapy lasting up to 48 weeks in patients aged 5 to 17 years, weight loss and growth inhibition were common (see ADVERSE REACTIONS). At 2 years post-treatment, 16% of pediatric patients were more than 15 percentiles below their baseline weight curve and 11% were more than 15 percentiles below their baseline height curve. The available longer term data on subjects who were followed up to 6 years post-treatment is too limited to determine the risk of reduced adult height in some patients. Safety and effectiveness have not been established in patients below the age of 18 (see INDICATIONS AND CLINICAL USE and Special Populations, Pediatrics).

Hematologic

Alpha interferons, including PEGASYS, may suppress bone marrow function which may result in severe cytopenias. Very rarely alpha interferons may be associated with pancytopenia including aplastic anemia. Therefore, caution should be exercised when administering PEGASYS in combination with other potentially myelosuppressive agents. It is advised that

complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

PEGASYS should be used with caution in patients with baseline absolute neutrophil counts (ANC) < 1.5 x 10^9/L, with baseline platelets < 90 x 10^9/L or baseline hemoglobin < 100 g/L. PEGASYS should be discontinued, at least temporarily, in patients who develop severe decreases in ANC (< 0.5 x 10^9/L) and/or platelet (< 25 x 10^9/L) counts (see DOSAGE AND ADMINISTRATION: Dose Adjustments).

Hepatic/Biliary/Pancreas

Hepatic

In patients who develop evidence of hepatic decompensation during treatment, PEGASYS treatment should be discontinued. HIV-HCV co-infected patients with advanced cirrhosis receiving concomitant HAART may be at an increased risk of hepatic decompensation and possibly death when treated with ribavirin in combination with alpha interferons, including PEGASYS. During treatment, co-infected patients should be closely monitored for signs and symptoms of hepatic decompensation (including ascites, encephalopathy, variceal bleeding, impaired hepatic synthetic function; (e.g. Child-Pugh score ≥ 6). The Child-Pugh scoring may be affected by factors related to treatment (i.e. indirect hyperbilirubinemia, decreased albumin) and not necessarily attributable to hepatic decompensation. Treatment with PEGASYS should be discontinued immediately in patients with hepatic decompensation (see DOSAGE AND ADMINISTRATION).

CHC: As with other alpha interferons, increases in ALT levels above baseline have been observed in patients treated with PEGASYS, including those patients who exhibit a virological response. When the increase in ALT levels is progressive despite dose reduction or is accompanied by increased bilirubin, therapy should be discontinued (see DOSAGE AND ADMINISTRATION).

CHB: Unlike CHC, disease exacerbations during therapy are not uncommon and are characterized by transient and potentially significant increases in serum ALT. Transient ALT elevations are common during CHB therapy with PEGASYS. Flares have been accompanied by elevations of total bilirubin and alkaline phosphatase and less commonly with prolongation of PT and reduced albumin levels. In clinical trials with PEGASYS in HBV, marked transaminase flares have been accompanied by mild changes in other measures of hepatic function and without evidence of hepatic decompensation. In approximately half the case of flares exceeding 10 times the upper limit of normal, PEGASYS dosing was reduced or withheld until the transaminase elevations subsided, while in the rest therapy was continued unchanged. More frequent monitoring of hepatic function was recommended in all instances (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Pancreatitis

Pancreatitis, sometimes fatal, has occurred during alpha interferon treatment. PEGASYS treatment should be suspended if symptoms or signs suggestive of pancreatitis are observed. PEGASYS should be discontinued in patients diagnosed with pancreatitis.

Hydration
Adequate hydration must be maintained in patients undergoing therapy with PEGASYS, since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Hypersensitivity
Serious, acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy and cutaneous eruptions (Stevens Johnson syndrome, toxic epidermal necrolysis) have been very rarely reported. If such a reaction develops during treatment with PEGASYS, treatment should be discontinued and appropriate medical therapy should be instituted immediately. Transient rashes do not necessitate interruption of treatment.

Immune
Exacerbation of autoimmune disease including myositis, hepatitis, immune thrombocytopenic purpura (ITP), rheumatoid arthritis, interstitial nephritis, thyroiditis and systemic lupus erythematosus has been reported in patients receiving alpha interferon therapy. PEGASYS is contraindicated in patients with a history of autoimmune disease. Use of alpha interferons has been associated with exacerbation or provocation of psoriasis. In case of appearance of psoriatic lesions, discontinuation of therapy should be considered.

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

Ophthalmologic
As with other interferons, retinopathy including retinal hemorrhages, cotton wool spots, papilledema, retinal artery or vein obstruction and serous retinal detachment have been reported in rare instances after treatment with PEGASYS. As with other interferons, decrease or loss of vision, macular edema and optic neuritis may be induced or aggravated by PEGASYS treatment. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during PEGASYS treatment. Any patient complaining of decreased or loss of vision must have a prompt and complete eye examination. PEGASYS treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Psychiatric
Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including PEGASYS. Depression, suicidal ideation, and suicidal attempt may occur in patients with and without previous psychiatric illness. Other CNS effects including aggressive behavior, confusion and other alterations of mental status have been observed with alpha interferon. PEGASYS should be used with extreme caution in patients who report a history of depression and physicians should monitor all patients (adults and pediatrics) for evidence of depression.

Physicians should inform patients of the possible development of depression prior to initiation of PEGASYS therapy, and patients should report any sign or symptom of depression immediately. If severe symptoms persist, therapy should be stopped and psychiatric intervention sought (see ADVERSE REACTIONS). Safety and effectiveness have not been established in patients below the age of 18 (see INDICATIONS AND CLINICAL USE and Special Populations, Pediatrics).

Patients with Substance Use/Abuse
HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc.) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alfa interferon. If treatment with alfa interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Renal
Renal impairment is associated with decreased total apparent clearance and prolonged half life. In subjects with a creatinine clearance between 0.33 and 0.67 mL/sec, the average total apparent clearance is reduced by approximately 30% compared with subjects with normal renal function following single doses of PEGASYS. There is no information available following multiple doses of drug, in patients with creatinine clearance < 0.83 mL/sec. As with all patients treated with PEGASYS, patients with renal impairment may require dose modification for moderate to severe adverse reactions (clinical and/or laboratory) occurring during therapy (see DOSAGE AND ADMINISTRATION: Dose Adjustments and ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics of PEGASYS in Special Populations and Conditions).

Respiratory
As with other alpha interferons, pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonia, pneumonitis, including fatality, and pulmonary hypertension have been reported during therapy with PEGASYS. Any patient developing fever, cough, and dyspnea or other respiratory symptoms must have a chest X ray taken. If there is evidence of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued. PEGASYS RBV should not be administered to patients with chronic obstructive pulmonary disease (COPD).

Sexual Function/Reproduction
Reproduction
Peginterferon alfa-2a has not been studied for its teratogenic effect. Treatment with interferon alfa-2a resulted in a statistically significant increase in abortifacient activity in rhesus monkeys; no teratogenic effects were seen in the offspring delivered at term (see Special Populations: Pregnant Women).

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

Special Populations
Pregnant Women: The safety of PEGASYS during pregnancy has not been established. Therefore, PEGASYS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

As with other alpha interferons, women of childbearing potential receiving PEGASYS therapy should be advised to use effective contraception during therapy (see Sexual Function/ Reproduction).

Nursing Women: It is not known whether PEGASYS or its components are excreted in human milk. The effect of orally ingested PEGASYS from breast milk on the nursing infant has not been evaluated. Because of the potential for adverse reactions from the drug in nursing infants, a decision should be made to discontinue nursing or PEGASYS, based on the importance of the therapy to the mother.

Pediatrics (< 18 years of age): Safety and effectiveness have not been established in patients below the age of 18. In addition, PEGASYS injection solutions contain benzyl alcohol. Therefore, PEGASYS should not be used in neonates or infants (see also INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS: Growth and Development (Pediatric Patients)).

Geriatrics (> 65 years of age): Clinical studies of PEGASYS alone or in combination with COPEGUS did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects.

Monitoring and Laboratory Tests
Before beginning PEGASYS therapy, standard hematological and biochemical profiles should be obtained for all patients. After initiation of therapy, hematological tests should be performed at 2 and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy.

The enrolment criteria used for the clinical studies of PEGASYS may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count $\geq 90 \times 10^9$/L (75×10^9/L in patients with cirrhosis or transition to cirrhosis)
- ANC $\geq 1.5 \times 10^9$/L
- Serum creatinine concentration < 1.5 x upper limit of normal
- TSH and T_4 within normal limits or adequately controlled thyroid function
- HIV-HCV co-infection: CD4+ ≥ 200/µl or CD4+ ≥ 100/µl - < 200/µl and HIV-1 RNA

<5000 copies/mL using Amplicor HIV-1 Monitor Test, v 1.5.

PEGASYS treatment was associated with decreases in both total white blood cell (WBC) count and ANC, usually starting within the first 2 weeks of treatment (see ADVERSE REACTIONS). In clinical studies, progressive decreases thereafter were infrequent. Dose reduction is recommended when ANC decreases to levels below 0.75 x 10^9/L (see DOSAGE AND ADMINISTRATION: Dose Adjustments). For patients with ANC values below 0.5 x 10^9/L treatment should be suspended until ANC values return to more than 1.0 x 10^9/L. In clinical trials with PEGASYS, the decrease in ANC was reversible upon dose reduction or cessation of therapy.

PEGASYS treatment was associated with decreases in platelet count, which returned to pre treatment (baseline) levels during the post treatment observation period (see ADVERSE REACTIONS). Dose reduction is recommended when platelet count decreases to levels below 50 x 10^9/L, and discontinuation of therapy is recommended when platelet count decreases to levels below 25 x 10^9/L (see DOSAGE AND ADMINISTRATION: Dose Adjustments).

Thyroid Changes: The occurrence of thyroid function abnormalities or the worsening of pre-existing thyroid disorders has been reported with the use of alpha interferon therapies, including PEGASYS RBV. Discontinuation of therapy should be considered in patients whose thyroid abnormalities cannot be adequately treated.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The frequency and severity of the most commonly reported adverse reactions are similar in patients treated with PEGASYS (peginterferon alfa-2a) and interferon alfa-2a.

The most frequently reported adverse reactions with 180 mcg PEGASYS were mostly mild to moderate in severity and were manageable without the need for modification of dosage or discontinuation of therapy.

Clinical Trial Adverse Drug Reactions

Chronic Hepatitis C Mono-infection

In mono-infection clinical trials, the incidence of withdrawal from treatment for all patients due to adverse events and laboratory abnormalities was 10%, 9% and 13% for interferon alfa-2a (IFN), PEGASYS or for PEGASYS RBV (peginterferon alfa-2a and ribavirin) combination therapy, respectively. Only 1% or 3% of patients required discontinuation of either PEGASYS or PEGASYS RBV combination therapy for laboratory abnormalities. The withdrawal rates for patients with cirrhosis were similar to those of the overall population.

HIV-HCV Co-infection

In HIV-HCV co-infected patients, the clinical adverse events reported on PEGASYS, PEGASYS RBV and interferon alfa-2a plus ribavirin were similar to that observed in HCV mono-infected patients.

In the co-infection study, the incidence of withdrawal from treatment for clinical adverse events, laboratory abnormalities or AIDS-defining events was 16% for PEGASYS monotherapy and 15% for both PEGASYS RBV and interferon alfa-2a plus ribavirin given for 48 weeks. Respectively, 4%, 3% or 1% of patients required discontinuation of PEGASYS or PEGASYS RBV or interferon alfa-2a plus ribavirin for laboratory abnormalities. In PEGASYS RBV combination therapy, the PEGASYS dose modification occurred in 39%, and the COPEGUS dose modification occurred in 37%, of the co-infected patients. In interferon alfa-2a plus ribavirin therapy, the interferon alfa-2a dose modification occurred in 16%, and the COPEGUS dose modification occurred in 28%, of the co-infected patients. In PEGASYS monotherapy, PEGASYS dose modification occurred in 38% of the co-infected patients. Serious adverse events were reported in 21%, 17% and 15% of those receiving PEGASYS monotherapy, PEGASYS RBV or interferon alfa-2a plus ribavirin, respectively.

Limited safety data (N= 31) is available in co-infected patients with CD4+ cell counts <200/µl treated with PEGASYS and PEGASYS RBV. PEGASYS containing treatment was associated with an on-treatment reduction in absolute CD4+ cell count without a reduction in CD4+ cell percentage. CD4+ cell count indices returned to baseline values during the follow-up period of the study. PEGASYS containing treatment had no apparent negative impact on the control of HIV viremia during therapy or follow-up.

Chronic Hepatitis B

In clinical trials of 48 week treatment and 24 weeks follow-up, the safety profile for PEGASYS in chronic hepatitis B (CHB) was similar to that seen in chronic hepatitis C, (see Table 1). 88% of patients treated with PEGASYS experienced adverse events, as compared to 53% of patients in the lamivudine comparator group, while 6% of the PEGASYS treated and 4% of the lamivudine treated patients experienced serious adverse events during the studies. Five percent of patients withdrew from treatment with PEGASYS due to adverse events or laboratory abnormalities, while less than 1% withdrew from lamivudine treatment for safety reasons. The withdrawal rates for patients with cirrhosis were similar to those of the overall population in each treatment group. The addition of lamivudine had no effect on the safety profile of PEGASYS.

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1a Adverse Reactions (≥10% of Incidence in Any Treatment Group).

	HBV		HCV						HIV-HCV	
	PEGASYS 180 mcg* N=448		Interferon alfa-2a 3 MIU N = 323		Interferon alfa-2a 6/3 MIU N = 261		PEGASYS 180 mcg N=827		INF alfa-2a 3 MIU + ribavirin 800 mg N=285		PEGASYS 180 mcg N=286	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Gastrointestinal												
Nausea	29	(6)	101	(31)	80	(31)	199	(24)	54	(19)	54	(19)
Diarrhea	28	(6)	44	(14)	48	(18)	132	(16)	29	(10)	35	(12)
Abdominal pain	19	(4)	50	(15)	35	(13)	120	(15)	17	(6)	18	(6)
Nausea and vomiting	9	(2)	19	(6)	25	(10)	43	(5)	22	(8)	18	(6)
General												
Fatigue	93	(21)	147	(46)	152	(58)	405	(49)	102	(36)	104	(36)
Rigors	28	(6)	134	(41)	112	(43)	219	(30)	49	(17)	41	(14)
Pyrexia	233	(52)	94	(29)	141	(54)	249	(35)	92	(32)	101	(35)
Injection site reaction	33	(7)	71	(22)	40	(15)	178	(22)	24	(8)	23	(8)
Pain	6	(1)	46	(14)	27	(10)	89	(11)	11	(4)	14	(5)
Asthenia	50	(11)	27	(8)	9	(3)	56	(7)	65	(23)	56	(20)
Metabolic and Nutritional												
Anorexia	59	(13)	37	(11)	61	(23)	131	(16)	71	(25)	59	(21)
Weight decreased	18	(4)	11	(3)	7	(3)	44	(5)	36	(13)	44	(15)
Musculoskeletal, Connective Tissue and Bone												
Myalgia	114	(25)	115	(36)	108	(41)	307	(37)	77	(27)	82	(29)
Arthralgia	43	(10)	87	(27)	82	(31)	211	(26)	36	(13)	43	(15)
Back pain	8	(2)	31	(10)	27	(10)	67	(8)	8	(3)	18	(6)
Neurological												
Headache	103	(23)	174	(54)	165	(63)	428	(52)	97	(34)	84	(29)
Insomnia	25	(6)	78	(24)	57	(22)	167	(20)	66	(23)	46	(16)
Dizziness (excluding vertigo)	28	(6)	33	(10)	39	(15)	120	(15)	26	(9)	7	(2)
Concentration impairment	9	(2)	31	(10)	26	(10)	76	(9)	7	(2)	7	(2)
Psychiatric												
Depression	17	(4)	51	(16)	57	(22)	148	(18)	57	(20)	45	(16)
Irritability	14	(3)	67	(21)	29	(11)	141	(17)	48	(17)	45	(16)
Skin and Subcutaneous Tissue												
Alopecia	78	(17)	78	(24)	92	(35)	187	(23)	13	(5)	19	(7)
Pruritus	25	(6)	20	(6)	24	(9)	104	(13)	11	(4)	12	(4)

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

Table 1b Adverse reactions reported in ≥1% to <10% on PEGASYS RBV combination or PEGASYS monotherapy in patients in clinical trials were:

	Any Treatment Group		HIV-HCV Only
Body system	**Common ≥ 5% to < 10%**	**Common ≥ 1% to < 5%**	**Other adverse reactions ≥ 1% to ≤ 3%**
Blood and lymphatic system disorders		lymphadenopathy, thrombocytopenia	
Cardiac disorders		palpitations,oedema peripheral, tachycardia	
Ear and labyrinth disorders		vertigo, earache, tinnitus	
Endocrine disorders		hypothyroidism , hyperthyroidism	
Eye disorders		vision blurred, eye inflammation, xerophthalmia, eye pain	
Gastrointestinal disorders	dry mouth, dyspepsia	mouth ulceration, flatulence, gingival bleeding, stomatitis, constipation, dysphagia, glossitis	cheilitis
General disorders and administration site conditions	malaise	lethargy, chest pain, hot flushes, thirst, influenza-like illness	
Infections and infestations		herpes simplex, URI infection bronchitis, oral candidiasis	influenza, pneumonia
Injury and poisoning		substance abuse	
Metabolism and nutrition disorders		dehydration	hyperlactacidemia /lactic acidosis
Musculoskeletal, connective tissue and bone disorders	back pain	muscle cramps, neck pain, musculoskeletal pain, bone pain, arthritis, muscle weakness	
Nervous system disorders	memory impairment	taste disturbance, weakness, paraesthesia, hypoaesthesia, tremor , migraine, somnolence, hyperaesthesia, nightmares, syncope	
Psychiatric disorders	anxiety, mood alteration, emotional disorders	nervousness, libido decreased, aggression, suicidal ideation, confusional state	affect lability, apathy
Renal and urinary disorders			chromaturia
Reproductive system and breast disorders		impotence	
Respiratory, thoracic and mediastinal disorders	dyspnoea, cough	sore throat, pharyngolaryngeal pain, dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, rhinitis, nasal congestion	
Skin and subcutaneous tissue disorders	rash, sweating increased	eczema, night sweats, psoriasis, photosensitivity reaction, urticaria, skin disorder	aquired lipodystrophy
Vascular disorders		flushing, hypertension	

As with other alpha interferon therapies, uncommon to rare cases (< 1%) of the following *serious* adverse events have been reported in patients receiving PEGASYS RBV combination or PEGASYS monotherapy during clinical trials:

Blood and the lymphatic system disorders: thrombotic thrombocytopenic purpura (TTP)
Cardiac disorders: arrhythmia, atrial fibrillation, pericarditis
Eye disorders: corneal ulcer
Gastrointestinal disorders: peptic ulcer, gastrointestinal bleeding, pancreatitis, abdominal distention
Immune system disorders: autoimmune phenomena (e.g. ITP, thyroiditis, psoriasis, rheumatoid arthritis, SLE), sarcoidosis
Infections and Infestations: skin infection, otitis externa, endocarditis
Hepato-biliary: hepatic dysfunction, fatty liver, cholangitis, malignant hepatic neoplasm
Nervous system disorders: myositis, peripheral neuropathy*, coma
Psychiatric disorders: suicide, panic attack, psychotic disorder, hallucination
Respiratory, thoracic and mediastinal disorders: interstitial pneumonitis with fatal outcome, pulmonary embolism
Vascular disorders: cerebral hemorrhage

Rarely, alpha interferon including PEGASYS RBV or PEGASYS monotherapy may be associated with pancytopenia, and very rarely, aplastic anemia has been reported.

Uncommon to very rare cases of hearing impairment (deafness) have been reported.

The adverse reactions observed with other alpha interferons may be expected with PEGASYS, including colitis and pancreatitis.

*In protocol NR15961 (HIV-HCV) the frequency was reported as 2% in the PEGASYS monotherapy arm.

Chronic Hepatitis C Pediatric Patients
In a clinical study, pediatric subjects treated with PEGASYS plus 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 subject weight and height decreased during treatment. At the end of 2 years follow-up after treatment, most subjects had returned to baseline normative curve percentiles for weight (64^{th} mean percentile at baseline, 60^{th} mean percentile at 2 years post-treatment) and height (54^{th} mean percentile at baseline, 56^{th} mean percentile at 2 years post-treatment). At the end of treatment, 43% (23 of 53) of subjects experienced a weight percentile decrease of more than 15 percentiles, and 25% (13 of 53) experienced a height percentile decrease of more than 15 percentiles on the normative growth curves. At 2 years post-treatment, 16% (6 of 38) of subjects were more than 15 percentiles below their baseline weight curve and 11% (4 of 38) were more than 15 percentiles below their baseline height curve.

55% (21 of 38) of subjects who completed the original study enrolled in the long-term follow up extending up to 6 years post-treatment. The study demonstrated that the post-treatment recovery in growth at 2 years post-treatment was maintained to 6 years post-treatment.Of the 4 subjects who were more than 15 percentiles below their baseline height curve at 2 years post-treatment, 2 entered the long-term follow-up study. They either returned to baseline comparable height percentiles at 6 years post-treatment (n=1) or a non-treatment related causative factor has been

identified (n=1). The available longer term data on subjects who were followed up to 6 years post-treatment is limited to determine the risk of reduced adult height in some patients Safety and effectiveness have not been established in patients below the age of 18 (see INDICATIONS AND CLINICAL USE and Special Populations, Pediatrics).

Abnormal Hematologic and Clinical Chemistry Findings

Hematology

As with other interferons, treatment with 180 mcg PEGASYS and PEGASYS RBV combination therapy was associated with decreases in hematological values, which generally improved with dosage modification and returned to pretreatment levels within 4 to 8 weeks upon cessation of therapy (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Although hematological toxicities of neutropenia, thrombocytopenia and anemia occurred more frequently in HIV-HCV patients, the majority could be managed by dose modification and the use of growth factors and infrequently required premature discontinuation of treatment.

Hemoglobin and Hematocrit: Treatment with 180 mcg PEGASYS and 3 MIU and 6/3 MIU interferon alfa-2a for HCV were associated with small gradual decreases in hemoglobin and hematocrit. Less than 1% of all patients treated with PEGASYS including those with cirrhosis, required dose modification for anemia (hemoglobin < 100 g/L). No patients receiving interferon alfa-2a required anemia-related dose modifications, due to drops in hemoglobin levels. Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Anemia (hemoglobin < 100 g/L) was observed in 13% of PEGASYS RBV combination-treated patients in clinical trials. The maximum drop in hemoglobin occurred during the first 8 weeks of initiation of ribavirin therapy (see DOSAGE AND ADMINISTRATION: Dose Adjustments).

Approximately 10% of patients on PEGASYS RBV combination therapy required COPEGUS dose modification for anemia. Patients receiving 800 mg of COPEGUS for 24 weeks had the lowest frequency of decrease in hemoglobin levels to < 100 g/L; hemoglobin levels did not fall to < 85 g/L in any of these patients.

Anemia (hemoglobin < 100g/L) was reported in 8% and 14% of HIV-HCV co-infected patients treated with PEGASYS monotherapy or PEGASYS RBV combination therapy, respectively.

White Blood Cells: Treatment with PEGASYS for HCV was associated with decreases in values for both total WBC and ANC. Transient decreases in ANC to levels below 0.5 x 10^9/L at some time during therapy, were observed in 3.8% and 5% of patients treated with PEGASYS and PEGASYS RBV versus 1.2% and 1.5% of patients treated with 3 MIU and 6/3 MIU interferon alfa-2a, respectively.

In HIV-HCV co-infected patients, 13% and 11% of those receiving PEGASYS monotherapy and PEGASYS RBV combination therapy, respectively, had decreases in ANC levels below 0.5 x $10^{9/}$L.

Platelet Count: Treatment with PEGASYS was associated with decreases in values for platelet counts. In HCV clinical trials for chronic hepatitis C, approximately 5% of patients had decreases in platelet counts to levels below 50 x 10^9/L versus 2.5% and 1.5% of patients in the 3 MIU and 3/6 MIU interferon alfa-2a treatment groups, respectively. Most of these patients were cirrhotic at baseline and/or entered the study with a baseline platelet count as low as 75 x 10^9/L.

In HIV-HCV patients, 10% and 8% of those receiving PEGASYS monotherapy and PEGASYS RBV combination therapy, respectively, had decreases in platelets below 50 x 10^9/L.

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

Clinical Chemistry
ALT: In clinical trials in CHB, 25% and 27% of patients experienced ALT elevations of 5 to 10 x the ULN and 12% and 18% exhibited elevations of >10 x ULN during treatment of HBeAg negative and HBeAg positive disease respectively. Overall, 11% of patients had dose modifications due to ALT flares and <1% of patients were withdrawn from treatment for this reason. ALT flares of 5-10 x ULN occurred in 13% and 16% of patients, while ALT flares of >10 x ULN occurred in 7% and 12% of patients in the HBeAG negative and HBeAG positive patients respectively, after discontinuation of PEGASYS therapy (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Thyroid Function: PEGASYS treatment was associated with clinically significant abnormalities in thyroid laboratory values requiring clinical intervention (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests). The frequencies observed with PEGASYS were similar to those observed with other interferons.

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

For a full listing of PEGASYS RBV combination adverse reactions, please refer to the current PEGASYS RBV product monograph.

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

Dehydration has been reported rarely with PEGASYS RBV combination therapy.

As with other alpha interferons, serous retinal detachment has been reported with PEGASYS RBV combination therapy.

As with other alpha interferons, liver and renal graft rejections have been reported on PEGASYS, alone or in combination with COPEGUS.

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

DRUG INTERACTIONS

Overview

No pharmacokinetic interactions between PEGASYS (peginterferon alfa-2a) and ribavirin have been observed in HCV clinical trials in which PEGASYS was used in combination with ribavirin. Similarly, lamivudine had no effect on PEGASYS pharmacokinetics in HBV clinical trials in which PEGASYS was used in combination with lamivudine.

Treatment with 180 mcg PEGASYS once weekly for 4 weeks had no effect on the pharmacokinetic profiles of tolbutamide (CYP 2C9), mephenytoin (CYP 2C19), debrisoquine (CYP 2D6), and dapsone (CYP 3A4) in healthy male subjects.

Drug-Drug Interactions

Table 2 Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical comment
Peginterferon alfa-2a and Methadone	CT	In a pharmacokinetic study of 24 HCV patients concomitantly receiving methadone maintenance therapy (median dose 95mg; range 30mg to 150mg), treatment with PEGASYS 180µg sc once weekly for 4 weeks was associated with mean methadone levels that were 10% to 15% higher than at baseline	The clinical significance of this finding is unknown; nonetheless, patients should be monitored for the signs and symptoms of methadone toxicity.
Peginterferon alfa-2a and Theophylline	T	PEGASYS is a modest inhibitor of cytochrome P450 1A2: a 25% increase in theophylline's AUC was observed in the same study. Comparable effects on the pharmacokinetics of theophylline have been seen after treatment with standard alpha interferons. Alpha interferons have been shown to affect the oxidative metabolism of some drugs by reducing the activity of hepatic microsomal cytochrome P450 enzymes.	Theophylline serum concentrations should be monitored and appropriate dose adjustments of theophylline made for patients taking theophylline and PEGASYS concomitantly.

Legend: C=Case Study; CT =Clinical Trial; T=Theoretical

Peginterferon alfa-2a and telbivudine

A non-Roche sponsored pilot clinical trial in Hepatitis B investigating the combination of telbivudine 600 mg daily, with pegylated interferon alfa -2a, 180 micrograms once weekly by subcutaneous administration, indicated that this combination is associated with an increased risk for developing **serious peripheral neuropathy** at a rate of 10%. An increased risk can not be ruled out for combination treatment with other interferon products (pegylated or standard). The benefit of telbivudine in combination with interferon alfa (pegylated or standard) is not currently established in patients. It is not recommended that telbivudine be given in combination with PEGASYS.

Drug-Herb Interactions
Pulmonary symptoms have been reported more frequently when sho-saiko-to, a Chinese herbal medicine, also known as Xiao-Chai-Hu was given with interferon alfa-2a. This herb should not be taken by patients receiving interferon.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

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

Treatment should be individualized to the patient depending on response to therapy and tolerability of the regimen.

Because the autoinjector is designed to deliver the full content, the autoinjector should only be used for patients who need the full dose. If the required dose is not available in an autoinjector, pre-filled syringes or vials should be used to administer the required dose.

Recommended Dose and Dosage Adjustment

Recommended Dose

Chronic Hepatitis C Mono-infection
The recommended dose of PEGASYS (peginterferon alfa-2a) is 180 mcg once-weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

HIV-HCV Co-infection
The recommended dosage of PEGASYS is 180 mcg once weekly subcutaneously for 48 weeks, regardless of genotype. The safety and efficacy of a duration of therapy less than 48 weeks has not been studied.

Early Predictability of Response: After 12 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any HCV (including HIV-HCV) patient who has not achieved viral clearance or an HCV-RNA reduction from baseline of at least 99% by week 12 (see CLINICAL TRIALS).

Chronic Hepatitis B
The recommended dose of PEGASYS (peginterferon alfa-2a) is 180 mcg once-weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

Dose Adjustments

General:

When dose modification is required for moderate to severe adverse reactions (clinical and/or laboratory), initial dose reduction to 135 mcg is generally adequate. However, in some cases, dose reduction to 90 mcg is necessary. Following improvement of the adverse reaction, dose increases to or toward the original dose may be considered (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Hematological:

Dose reduction to 135 mcg PEGASYS is recommended if the ANC is less than 7.5 x 10^9/L. For patients with ANC values below 0.5 x 10^9/L, treatment should be suspended until ANC values return to over 1.0 x 10^9/L. Therapy should initially be reinstituted at 90 mcg PEGASYS, and the ANC monitored.

Dose reduction to 90 mcg PEGASYS is recommended if the platelet count is less than 50 x 10^9/L. Cessation of therapy is recommended when platelet count decreases to levels below 25 x 10^9/L.

Liver Function:

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

For CHC patients, the dose should be reduced initially to 90 mcg in the presence of progressive ALT increases above baseline values. When increase in ALT levels is progressive despite dose reduction, or is accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued.

For CHB patients, transient flares of ALT levels sometimes exceeding 10 times the upper limit of normal are not uncommon, and may reflect immune clearance. Consideration should be given to continuing treatment with more frequent monitoring of liver function during ALT flares. If the PEGASYS dose is reduced or withheld, therapy can be restored once the flare is subsiding (see WARNINGS AND PRECAUTIONS)

Depression:

PEGASYS should be used with extreme caution in patients who report a history of depression and physicians should monitor all patients for evidence of depression. For mild depression, no dose adjustment is necessary. For moderate depression, an initial dose reduction to 135 mcg is recommended; however, dose reduction to 90 mcg may be needed. Patients should be closely monitored. The frequency and nature of the monitoring should be based on the clinical judgment of the physician. If severe symptoms persist, therapy should be stopped and psychiatric intervention sought (see WARNINGS AND PRECAUTIONS).

Special Populations

Renal Impairment: No dose adjustments in the recommended starting dose of PEGASYS 180 mcg once weekly is required in patients with creatinine clearance > 0.33 mL/sec. In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored.

In subjects with end-stage renal disease requiring hemodialysis, a starting dose of 135 mcg should be used. Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of PEGASYS during the course of therapy should be made in the event of adverse reactions (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations and Conditions).

Geriatric Use: No special dosage modification is required for geriatric patients with normal renal function, based upon pharmacokinetic, pharmacodynamic, tolerability, and safety data from clinical trials.

Hepatic Impairment:
PEGASYS has been shown to be effective and safe in patients with compensated cirrhosis (e.g. Child-Pugh A). PEGASYS has not been studied in patients with decompensated liver disease (e.g. Child-Pugh B/C or bleeding esophageal varices) (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

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.

Table 3 Modified Assessment

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

Grading according to Trey, Burns and Saunders (1966)

Missed Dose
If the PEGASYS dose is missed and remembered within 2 days of the scheduled dose, the PEGASYS dose should be administered as soon as possible. The next scheduled PEGASYS dose should be given on the usual day. If more than 2 days have elapsed, the dosage schedule should be based on the clinical judgment of the physician.

Administration
Use a sterile needle and syringe to prepare PEGASYS. PEGASYS (peginterferon alfa-2a) is administered subcutaneously in the abdomen or thigh once -weekly (see DOSAGE AND ADMINISTRATION, Recommended Dose). Visually inspect the solution prior to administration. Do not use if discoloured or if particles are present.

OVERDOSAGE

There is limited experience with overdosage. The maximum dose received by any patient was 7 times the intended dose of PEGASYS (peginterferon alfa-2a), (180 mcg/day for 7 days). There were no serious reactions attributed to overdosages. Weekly doses of up to 630 mcg have been administered to patients with cancer. Dose limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia. There is no specific antidote for PEGASYS. Hemodialysis and peritoneal dialysis are not effective.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
PEGASYS (peginterferon alfa-2a) possesses the in vitro antiviral and antiproliferative activities of interferon alfa-2a. Interferons bind to specific receptors on the cell surface initiating a complex intracellular signalling pathway and rapid activation of gene transcription. Interferon-stimulated genes modulate many biological effects including the inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation. The clinical relevance of these in vitro activities is not known.

Pharmacodynamics
HCV RNA levels decline in a biphasic manner in responding patients with hepatitis C with and without compensated cirrhosis who have received treatment with 180 mcg PEGASYS. The first phase of decline occurs within 24 to 36 hours after the first PEGASYS dose in sustained responders and in some patients that do not achieve a sustained virological response. In those individuals who are sustained responders, the second phase of decline occurs over the next 4 to 16 weeks. Treatment with 180 mcg PEGASYS per week enhances the virion clearance and improves the virological end of treatment responses compared to treatment with interferon alfa-2a.

PEGASYS stimulates the production of effector proteins such as serum neopterin, 2', 5'-oligoadenylate synthetase (2',5'-OAS), raises body temperature and causes reversible decreases in leukocyte and platelet counts. The stimulation of 2',5'-OAS is maximal after single doses of 135 to 180 mcg PEGASYS and stays maximal throughout the one week dosing interval. The magnitude and duration of 2',5'-OAS activity induced by PEGASYS were reduced in subjects older than 62 years and in subjects with significant renal impairment (creatinine clearances of 0.33 to 0.67 mL/sec) compared to that seen in healthy subjects. The correlation between the *in vitro* and *in vivo* pharmacology and pharmacodynamic and clinical effects is unknown.

Pharmacokinetics

The structure of the PEG moiety directly affects the clinical pharmacology of PEGASYS. Specifically, the size, branching and location of attachment of the 40 kD PEG moiety contribute to defining the absorption, distribution and elimination characteristics of PEGASYS. The pharmacokinetics of PEGASYS were studied in healthy volunteers and hepatitis C virus (HCV) - infected patients. The results for patients with chronic hepatitis B were similar to those for patients with chronic hepatitis C.

Absorption: The absorption of PEGASYS is sustained with peak serum concentrations reached 72 to 96 hours after dosing. Serum concentrations are measurable within 3 to 6 hours of a single dose. Dose proportional increases in AUC and C_{max} are seen in patients that received once weekly doses of PEGASYS.

The absolute bioavailability of PEGASYS following sc administration in the abdomen is 84% and is similar to that seen with interferon alfa-2a.

Distribution: The volume of distribution at steady-state (V_{ss}) of 6 to 14 liters after intravenous dosing suggests that the drug is found mainly in the bloodstream and extracellular fluid.

Metabolism: The metabolic profile of PEGASYS is not fully characterized. See also PHARMACOLOGY, Nonclincal Pharmacokinetics.

Excretion: The systemic clearance of PEGASYS is about 100 mL/h, which is 100-fold lower than that of interferon alfa-2a. After an intravenous dose, the terminal half-life of PEGASYS in healthy subjects is about 60 hours compared to 3 to 4 hours for standard interferon. The terminal half-life after subcutaneous administration in patients is longer with a mean value of 160 hours (84 to 353 hours). The terminal half-life after subcutaneous dosing may be reflecting the sustained absorption of PEGASYS and not the elimination of the drug.

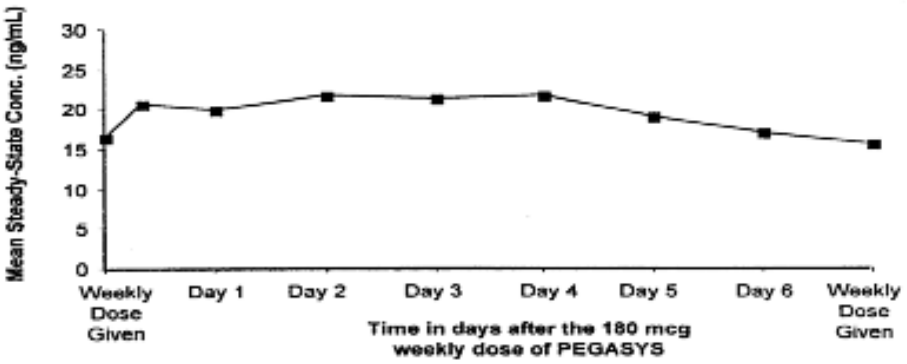
The kidneys eliminate less than 10% of a dose as the intact peginterferon alfa-2a. The rest is broken down metabolically.

Steady state serum levels are reached within 5 to 8 weeks of once-weekly dosing. Once steady state has been achieved, there is no accumulation of peginterferon alfa-2a. The peak to trough ratio after 48 weeks of treatment is about 1.5 to 2.0. Peginterferon alfa-2a serum concentrations are sustained throughout the 1 week dosing interval (168 hours) [Table 5 and Figure 1].

Table 4 Pharmacokinetic parameters of PEGASYS after single and multiple dose of 180 mcg

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

Figure 1. Mean steady-state PEGASYS concentrations in patients with CHC



Special Populations and Conditions

Pediatrics (<18 years of age): The pharmacokinetics of PEGASYS have not been adequately studied in pediatric patients.

Geriatrics: In subjects older than 62 years, the AUC was modestly increased (1663 vs 1295 ng·h/mL, older than 62 years vs younger, respectively), but peak concentrations (9.1 vs 10.3 ng/mL) were similar in the two age groups (see DOSAGE AND ADMINISTRATION).

Gender: The pharmacokinetics of PEGASYS after single subcutaneous injections were comparable between male and female healthy subjects.

Race: In a pharmacokinetic study in 40 CHC patients, no ethnicity-based differences in PEGASYS pharmacokinetic parameters were observed between Black (n=13) and Caucasian (n=15) patients or Hispanic (n=12) and Caucasian patients.

Hepatic Insufficiency: The pharmacokinetics of PEGASYS were similar between healthy subjects and patients with chronic hepatitis B or chronic hepatitis C. Comparable pharmacokinetic profiles were seen in cirrhotic patients with compensated liver disease and patients without cirrhosis.

Renal Insufficiency: Renal impairment is associated with decreased total apparent clearance and prolonged half-life. In subjects with a creatinine clearance between 0.33 and 0.67 mL/sec, the average total apparent clearance is reduced by approximately 30% compared with subjects with normal renal function following single doses of PEGASYS.

In subjects with end-stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance of peginterferon alfa-2a and doses of 135 mcg provide exposure similar to those observed in subjects with normal renal function receiving 180 mcg doses. Regardless of the starting dose or degree of renal impairment, patients should be monitored and appropriate dose reductions of PEGASYS during the course of therapy should be made in the event of adverse reactions (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION: Dose Adjustments).

Genetic Polymorphism: Different HCV genotypes display considerable clinical variability in their response to PEGASYS and COPEGUS. Viral genetic determinants associated with the variable response have not been definitively identified.

STORAGE AND STABILITY

Stability and Storage Recommendations:
Store in refrigerator at 2-8°C. Protect from light. Do not freeze or shake. Do not use PEGASYS (peginterferon alfa-2a) beyond the date of expiry.

Parenteral drug products such as PEGASYS should be inspected visually for particulate matter and discolouration before administration. Do not use PEGASYS if it contains particulate matter or it appears discoloured.

SPECIAL HANDLING INSTRUCTIONS

PEGASYS (peginterferon alfa-2a)

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

- Needles and syringes should never be reused.

- Place all used needles, autoinjectors and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider

For home use, a puncture resistant container for the disposal of used syringes, autoinjectors and needles should be supplied to the patients.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage forms:
PEGASYS (peginterferon alfa-2a) is a sterile, ready-to-use solution for subcutaneous injection.

Composition:
PEGASYS Pre-filled Syringe: Each 0.5 mL contains 180 mcg of peginterferon alfa-2a (expressed as the amount of interferon alfa-2a), 4.0 mg sodium chloride, 0.025 mg polysorbate 80, 5.0 mg benzyl alcohol, 1.3085 mg sodium acetate trihydrate, 0.0231 mg acetic acid and water for injection, at pH 6 ± 0.2.

PEGASYS Vial: Each 1 mL vial contains 180 mcg of peginterferon alfa-2a (expressed as the amount of interferon alfa-2a), 8.0 mg sodium chloride, 0.05 mg polysorbate 80, 10.0 mg benzyl alcohol, 2.617 mg sodium acetate trihydrate, 0.0462 mg acetic acid and water for injection, at pH 6 ± 0.2.

PEGASYS ProClick® Autoinjector: Each 0.5 mL contains 180 mcg of peginterferon alfa-2a (expressed as the amount of interferon alfa-2a), 4.0 mg sodium chloride, 0.025 mg polysorbate 80, 5.0 mg benzyl alcohol, 1.3085 mg sodium acetate trihydrate, 0.0231 mg acetic acid and water for injection, at pH 6 ± 0.2.

The ready to use autoinjector includes a post-injection needle shield that was designed to help prevent needle-stick injuries and keeps the needle non-visible.

Packaging:
PEGASYS is supplied as 180 mcg/0.5 mL in single-use, graduated, clear glass pre-filled syringes in packages of 1 and 4.

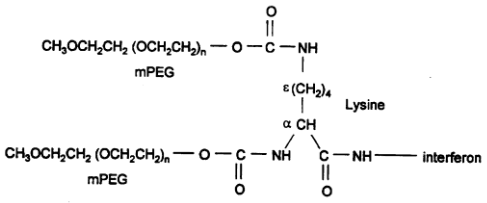
PEGASYS is also supplied as 180 mcg/mL in single-use, clear glass vials in packages of 1 and 4.

PEGASYS ProClick® is supplied as 180 mcg/0.5 mL in single-use, disposable autoinjectors in packages of 1 and 4.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	Peginterferon alfa-2a (INN)
Chemical Name	Bis-(N-monomethoxypolyethyleneglycol-urethanyl) lysyl interferon alfa-2a.
Molecular formula and molecular mass	Peginterferon alfa-2a is made by conjugating a single branched polyethylene glycol chain (PEG), of approximate molecular weight of 40,000 dalton, to interferon alfa-2a (20,000 dalton) via a stable amide bond. Interferon alfa-2a is a monomeric protein containing 165 amino acids with a molecular formula $C_{860}H_{1349}N_{227}O_{255}S_9$.
Structural Formula	
Physicochemical properties:	Colourless to light yellow solution
Other Properties	-

CLINICAL TRIALS

Chronic Hepatitis C Mono-infection

The safety and effectiveness of PEGASYS (peginterferon alfa-2a) for the treatment of hepatitis C mono-infection were assessed in three randomized, open label, active controlled clinical studies. All patients were adults and had compensated liver disease and detectable hepatitis C virus (HCV), and were previously untreated with interferon. All patients received therapy by sc injection for 48 weeks, and were followed for an additional 24 weeks to assess the durability of response. In studies 1 and 2, approximately 20% of subjects had cirrhosis or transition to cirrhosis. Study 3 was designed to enrol only patients with a histological diagnosis of cirrhosis or transition to cirrhosis.

Table 5 Summary of patient demographics for clinical trials for the treatment of Chronic Hepatitis C

Study #	Trial Design	Dosage, route of administration and duration	Number	Gender	Mean age (Range)	% HCV Genotype Type 1
Study 1	Randomized, open-label, parallel-group, multicenter	IFN 3 MIU, sc, three times a week for 48-wk trt period followed by 24 wks untreated follow-up;	214	Male/Female (131/83)	42.8 years (20 - 69)	64%
		PEGASYS 135 mcg, sc, once each week for 48-wk trt period followed by 24 wks untreated follow-up;	215	Male/Female (157/58)	41.5 years (18 – 72)	64%
		PEGASYS 180 mcg, sc, once each week for 48-wk trt period followed by 24 wks untreated follow-up.	210	Male/Female (149/61)	42.7 years (28 - 71)	70%
Study 2	Randomized, open-label, parallel-group, multicenter	IFN 6 MIU, sc three times/week for 12 weeks followed by 3 MIU, sc, three times/week for 36 weeks for 48-wk trt period followed by 24 wks untreated follow-up;	264	Male/Female (176/88)	41 years (21 – 70)	61%
		PEGASYS 180 mcg, sc, once each week for 48-wk trt period followed by 24 wks untreated follow-up.	267	Male/Female (178/89)	40.6 years (19 – 72)	63%
Study 3	Randomized, open-label, parallel-group, multicenter	IFN 3 MIU, sc, three times/week, for 48-wk trt period followed by 24 wks untreated follow-up;	88	Male/Female (62/26)	46.9 years (28 - 76)	53%
		PEGASYS 90 mcg, sc, once each week for 48-wk trt period followed by 24 wks untreated follow-up;	96	Male/Female (71/25)	47.2 years (28 - 76)	61%
		PEGASYS 180 mcg, sc, once each week for 48-wk trt period followed by 24 wks untreated follow-up.	87	Male/Female (63/24)	47.1 years (29-76)	55%

In study 1, 639 patients were enrolled and received either interferon alfa-2a 3 MIU three times/week, PEGASYS 135 mcg once each week, or PEGASYS 180 mcg once each week. In study 2, 531 patients were enrolled and received either interferon alfa-2a 6 MIU three times/week for 12 weeks followed by 3 MIU three times/week for 36 weeks or PEGASYS 180 mcg once each week.

In study 3, 271 patients were enrolled and received interferon alfa-2a 3 MIU three times/week, PEGASYS 90 mcg once each week, or PEGASYS 180 mcg once each week.

Response to treatment was defined as undetectable HCV RNA and normalization of ALT on or after 20 weeks post-treatment. The virological and biochemical responses of the 180 mcg PEGASYS and comparator arms are summarized in Table 6.

Table 6 Rates of Response to Treatment*

	Study 1		Study 2		Pooled Data Studies 1 and 2		Study 3 (with Cirrhosis)	
	Interferon alfa-2a	PEGASYS	Interferon alfa-2a	PEGASYS	Interferon alfa-2a	PEGASYS	Interferon alfa-2a	PEGASYS
	3 MIU (N=214)	180 mcg (N=210)	6 MIU/3 MIU (N=264)	180 mcg (N=267)	3 MIU or 6/3 MIU (N=505)	180 mcg (N=477)	3 MIU (N=88)	180 mcg (N=87)
Combined Sustained Responder (wk 72)	23 (11%)	55 (26%) p=0.001	46 (17%)	101 (38%) p=0.001	69 (14%)	156 (33%) p=-0.001	7 (8%)	26 (30%) p=0.001
Biochemical Sustained Responder (wk 72)	38 (18%)	66 (31%) p=0.001	65 (25%)	120 (45%) p=0.001	103 (22%)	186 (39%) p=0.001	13 (15%)	30 (34%) p=0.004
Virological Sustained Responder (wk 72)	23 (11%)	58 (28%) p=0.001	50 (19%)	103 (39%) p=0.001	73 (15%)	161 (34%) p=0.001	7 (8%)	26 (30%) p=0.001
Genotype 1**	(N=138) 9 (7%)	(N=148) 32 (22%)	(N=161) 12 (7%)	(N=168) 47 (28%)	(N=299) 21 (7%)	(N=316) 79 (25%)	(N=47) 1 (2%)	(N=48) 6 (13%)
Genotype non-1** Genotype 2/3**	(N=74) 14 (19%)	(N=61) 25 (41%)	(N=101) 37 (37%)	(N=98) 55 (56%)	(N=175) 51 (29%)	(N=159) 80 (50%)	(N=40) 6 (15%)	(N=36) 19 (53%)
Virological Response End of Treatment (wk 48)	47 (22%)	115 (55%) p=0.001	73 (28%)	185 (69%) p=0.001	120 (25%)	300 (63%) p=0.001	12 (14%)	38 (44%) p=0.001

*Virological response at any time point was defined as undetectable HCV RNA as measured by the Amplicor HCV MonitorJ, version 2 (limit of detection 100 copies/mL equivalent to 50 International Units/mL).
**Patients in the ITT population of unknown genotype are not included.
Note: p values assessed by Cochran-Mantel-Haenszel Test stratified by center.

Patients treated with 180 mcg PEGASYS had overall sustained virological responses of 30% in patients with cirrhosis or developing cirrhosis and 35% in patients without cirrhosis.

Matched pre- and post-treatment liver biopsies were obtained in approximately 70% of patients. Similar modest reductions in inflammation and fibrosis compared to baseline were observed in all treatment groups.

Of patients who did not demonstrate by 12 weeks of PEGASYS 180 mcg therapy, either undetectable HCV RNA or at least a 2-log10 drop in HCV RNA titer from baseline, 2% achieved a sustained virological response (see DOSAGE AND ADMINISTRATION). Of note, only 3% of patients treated with 180 mcg PEGASYS in clinical trials required premature withdrawal through 12 weeks of therapy because of adverse experiences.

The treatment response rates were similar in men and women and in non-Caucasians compared to Caucasians. However, the total number of non-Caucasian patients was too small to rule out substantial differences.

In all studies, most patients treated with PEGASYS have normalization or improvement of serum ALT during therapy. However, ALT may not normalize, even in patients in whom HCV RNA has become undetectable, until after PEGASYS treatment has been completed. Whether or not ALT normalizes, virological determination provides a more reliable means of determining the

effectiveness of PEGASYS treatment.

Anti-Interferon Antibodies: Only 1% and 2% of patients treated with 180 mcg PEGASYS developed neutralizing anti-interferon antibodies in studies 1 and 2, respectively.
A phase III randomized, multicenter, placebo-controlled study (study 4) was conducted in chronic hepatitis C patients (N= 1121). Patients received treatment with the combination of peginterferon alfa-2a and ribavirin, the combination of interferon alfa-2b and ribavirin or peginterferon alfa-2a monotherapy. The safety profile observed was consistent with the expected effects of the individual compounds. There was no evidence that the co-administration of ribavirin influenced the pharmacokinetics of peginterferon alfa-2a.

Table 7 Summary of patient demographics for clinical trials for the treatment of Chronic Hepatitis C mono-infection

Study #	Trial Design	Dosage, route of administration and duration	Number	Gender	Mean age (Range)	% HCV Genotype 1
Study 4	Randomized, multicentre, partially blinded, active-controlled and placebo-controlled study.	PEGASYS 180 mcg sc once weekly with placebo, oral for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.	224	Male/Female (151/73)	42.4 years (19 – 64)	65%
		PEGASYS 180 mcg sc once weekly with COPEGUS 1000 mg, oral (body weight <75 kg) or 1200 mg (body weight ≥ 75 kg) for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.	453	Male/Female (324/129)	42.8 years (19 – 76)	66%
		Interferon alfa-2b plus ribavirin (active control), oral for 48 weeks of therapy followed by 24 weeks of treatment-free follow-up.	444	Male/Female (325/119)	42.3 years (20 – 71)	64%

HIV-HCV Co-Infection

In the co-infection clinical trial, study 5, 859 HIV-HCV co-infected patients were randomized and treated with PEGASYS, PEGASYS RBV or interferon alfa-2a 3 MIU three times weekly and ribavirin 800 mg/day for 48 weeks followed by a 24 week treatment free follow-up. The sustained virologic responses for the three treatment groups are summarized for all patients and by genotype in Table 9.

Table 8 Summary of patient demographics for clinical trials in HCV-HIV co-infection

Study #	Trial Design	Dosage, route of administration and duration	Number	Gender	Mean age (Range)	% HCV Genotype 1
Study 5	randomized, multicentre, partially blinded, active-controlled and placebo-controlled study and drug interaction nested trial between PEG-IFN alfa-2a and protease inhibitors.	PEGASYS 180 mcg/week and placebo for 8 weeks followed by a 24 week treatment free follow-up.	286	Male/Female (234/52)	40.0 years (22 – 66)	61%
		PEGASYS 180 mcg/week and COPEGUS 800 mg/day for 48 weeks followed by a 24 week treatment free follow-up.	288	Male/Female (232/57)	39.7 years (20 – 64)	61%
		Interferon alfa-2a 3 MIU three times weekly and ribavirin 800 mg/day for 48 weeks followed by a 24 week treatment free follow-up.	285	Male/Female (231/54)	40.1 years (18 – 74)	60%

Table 9 Sustained Virologic Response in HIV-HCV Co-infected Patients

	PEGASYS 180mcg + Placebo 48 weeks	PEGASYS 180mcg + COPEGUS 800 mg 48 weeks	Interferon alfa-2a 3MIU + COPEGUS 800 mg 48 weeks
All patients	20% (58/286)*	40% (116/289)*	12% (33/285)*
Genotype 1	14% (24/175)	29% (51/176)	7% (12/171)
Genotype 2/3	36% (32/90)	62% (59/95)	20% (18/89)

* PEGASYS 180mcg COPEGUS 800mg *vs*. Interferon alfa-2a 3MIU COPEGUS 800mg: Odds Ratio (95% CI) = 5.40 (3.42 to 8.54) p-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* PEGASYS 180mcg COPEGUS 800mg *vs*. PEGASYS 180mcg: Odds Ratio (95% CI): 2.89 (1.93 to 4.32), p-value (stratified Cochran-Mantel-Haenszel test) = < 0.0001

* Interferon alfa-2a 3 MIU COPEGUS 800 mg vs. PEGASYS 180mcg: Odds Ratio (95% CI): 0.53 (0.33 to 0.85), p-value (stratified Cochran-Mantel-Haenszel test) = < 0.0084

Predictability of Response

Patients who do not demonstrate an early virological response (defined as achieving undetectable levels of HCV RNA or at least a 99% reduction in viral titer from baseline by the end of 12 weeks of treatment) to PEGASYS monotherapy therapy are unlikely to achieve a SVR at week 72 with continuation of treatment. In co-infection clinical study 5, the negative predictive value that has been observed in HIV-HCV co-infected patients treated with PEGASYS was (100%). Positive predictive value of 33% and 41% were observed for genotype 1 and genotype 2/3 HIV-HCV co-infected patients receiving PEGASYS monotherapy, respectively.

Chronic Hepatitis B

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

All clinical trials recruited patients with chronic hepatitis B who had active viral replication measured by HBV DNA, elevated levels of ALT and a liver biopsy consistent with chronic hepatitis. Study 6 recruited patients who were positive for HBeAg, while study 7 recruited patients who were negative for HBeAg and positive for anti-HBe. In both studies the treatment duration was 48 weeks, with 24 weeks of treatment-free follow-up. Both studies compared PEGASYS plus placebo vs PEGASYS plus lamivudine vs lamivudine alone. No HBV-HIV co-infected patients were included in these clinical trials.

Table 10 Summary of patient demographics for clinical trials in CHB

Study #	Trial Design	Dosage, route of administration and duration	Number	Gender	Mean age (Range)
Study 6 (HBeAg-positive CHB)	Multicenter, randomized, open-label lamivudine monotherapy and open-label PEGASYS, partially-blinded with respect to lamivudine or placebo in combination with PEGASYS.	PEGASYS 180 µg sc 1 qw + placebo, 48 weeks of treatment plus 24 weeks of untreated follow-up.	271	Male/Female (214/57)	32.5 years (18 – 77)
		PEGASYS180 µg sc 1 qw + lamivudine 100 mg daily po, 48 weeks of treatment plus 24 weeks of untreated follow-up.	271	Male/Female (208/63)	31.7 years (18 – 66)
		Lamivudine 100 mg daily po., 48 weeks of treatment plus 24 weeks of untreated follow-up.	272	Male/Female (215/57)	31.6 years (17 – 65)
Study 7 (HBeAg-negative CHB)	Multicenter, randomized, open-label lamivudine monotherapy and open-label PEGASYS, partially-blinded with respect to lamivudine or placebo in combination with PEGASYS	PEGASYS 180 µg sc 1 qw + placebo , 48 weeks of treatment plus 24 weeks of untreated follow-up.	177	Male/Female (151/26)	40.1 years (18 – 71)
		PEGASYS 180 µg sc 1 qw + lamivudine 100 mg po daily , 48 weeks of treatment plus 24 weeks of untreated follow-up.	179	Male/Female (147/32)	40.5 years (18 – 70)
		Lamivudine 100 mg daily po., 48 weeks of treatment plus 24 weeks of untreated follow-up.	180	Male/Female (156/25)	39.8 years (18 – 66)

Response rates at the end of follow-up for the two studies are presented in Table 11. HBV DNA was measured by the COBAS AMPLICOR HBV MONITOR Assay (limit of detection 200 copies/mL).

Table 11 Serological, Virological and Biochemical Responses in Chronic Hepatitis B

	HBeAg positive Study 6			**HBeAg negative / anti-HBe positive Study 7**		
	Pegasys 180 mcg & **Placebo** (N=271)	**Pegasys** 180 mcg & **Lamivudine** 100 mg (N=271)	**Lamivudine** 100 mg (N=272)	**Pegasys** 180 mcg & **Placebo** (N=177)	**Pegasys** 180 mcg & **Lamivudine** 100 mg (N=179)	**Lamivudine** 100 mg (N=181)
HBeAg Sero-conversion	32% [1]	27%	19%	N/A	N/A	N/A
HBV DNA*	32% [2]	34%	22%	43% [5]	44%	29%
ALT Normal-ization	41% [3]	39%	28%	59% [6]	60%	44%
HBsAg Sero-conversion	3% [4]	3%	0%	3%	2%	0%

* For HBeAg-positive patients: HBV DNA < 10^5 copies/ml
For HBeAg-negative /anti-HBe-positive patients: HBV DNA < 2 x 10^4 copies/ml

[1] Odds Ratio (95% CI) vs lamivudine = 2.00 (1.34 – 2.97) p-value (stratified Cochran-Mantel-Haenszel test) < 0.001
[2] Odds Ratio (95% CI) vs lamivudine = 1.64 (1.12 – 2.42) p-value (stratified Cochran-Mantel-Haenszel test) = 0.012
[3] Odds Ratio (95% CI) vs lamivudine = 1.77 (1.23 – 2.54) p-value (stratified Cochran-Mantel-Haenszel test) = 0.002
[4] Odds Ratio not definable p-value (stratified Cochran-Mantel-Haenszel test) = 0.004
[5] Odds Ratio (95% CI) vs lamivudine = 1.84 (1.17 – 2.89) p-value (stratified Cochran-Mantel-Haenszel test) = 0.007
[6] Odds Ratio (95% CI) vs lamivudine = 1.86 (1.22 – 2.85) p-value (stratified Cochran-Mantel-Haenszel test) = 0.004

The overall incidence of neutralizing anti-interferon antibodies was 7.6% and 4.5% for study 6 and study 7 respectively.

PEGASYS coadministered with Lamivudine did not result in any additional sustained response when compared to PEGASYS monotherapy.

DETAILED PHARMACOLOGY

PEGASYS (peginterferon alfa-2a)

Nonclinical Pharmacology

The preclinical studies have demonstrated that peginterferon alfa-2a (PEG-IFN) retains the ability to bind to the alpha interferon receptor, to activate interferon-induced signaling pathways, and to stimulate the expression of a known interferon-inducible human gene *in vitro*. PEG-IFN has also been shown to retain antiviral and antiproliferative properties typical of an alpha interferon. These *in vitro* data support the hypothesis that the biological activity of interferon alfa-2a (IFN) is retained following the pegylation process and is mediated by the IFN portion of the PEG-IFN molecule, acting via a classical alpha interferon pathway.

The *in vivo* studies demonstrate that PEG-IFN retains biological activity as shown by induction of 2,5-OAS activity in the monkey and by reduction of tumor xenograft growth and regression in the mouse. The comparison of once weekly administration of PEG-IFN with three times weekly administration of IFN in the mouse model demonstrates that the *in vivo* biological activity of PEG-IFN is enhanced compared with IFN.

Safety pharmacology studies were conducted to evaluate the effects of PEG-IFN on the cardiovascular, respiratory, renal, gastrointestinal and central nervous systems. Decreases in urine volume accompanied by decreases in urinary potassium levels were noted after sc administration of PEG-IFN to saline-loaded rats. In cynomolgus monkeys a slight tachycardia was observed following iv administration of PEG-IFN.

Studies designed to investigate the apparent neutropenia observed in clinical studies following PEG-IFN administration, and to show the effect of administration of G-CSF (filgrastim) on neutrophil counts, were conducted in female mice. Due to the species specificity of IFN, a pegylated form of hybrid human IFN (PEG-IFNαA/D), which is active on murine cells was used.

Treatment of female mice with PEG-IFNαA/D resulted in lymphopenia in the peripheral blood and to a lesser extent in the bone marrow. In addition, neutropenia, reticulocytopenia and thrombocytopenia were observed in the peripheral blood. Treatment with filgrastim on days 2 and 3 ameliorated the neutropenia caused by a single dose of PEG-IFNαA/D.

TOXICOLOGY

PEGASYS (Peginterferon alfa-2a)

The preclinical toxicology data demonstrate that the modification of the interferon alfa-2a (IFN) molecule by pegylation (PEG-IFN) does not induce additional or unexpected toxicity beyond that previously observed with interferons. The following were the main findings:

A 4-week toxicity study was performed in cynomologus monkeys using twice weekly sc dosing to give dose levels of 30, 375, and 1125 mcg/kg/week. Only mild effects were observed and these were limited to transient clinical pathology changes at the mid and high doses. Toxicological findings were limited to the following: slight transient hematological changes (i.e., decreased platelet and WBC counts) and slight transient clinical chemistry changes, including decreases in protein, calcium, and, in a few animals, elevated ALT and/or AST (1.4 to 2.3 times baseline) values. In a 13-week study of similar design, comparable results for the decreases in platelets, WBC and protein were seen at all three dose levels (30, 100 and 300 mcg/kg/week).

The toxicity profile of PEG-IFN was further characterized in a 4-week daily dose study employing sc doses of 15, 100, and 600 mcg/kg/day. Changes similar to those described above but with more pronounced effects were observed. In one female monkey receiving 600 mcg/kg/day, pronounced adverse effects, clinical signs, and clinical pathology changes (regenerative anemia, leukopenia, thrombocytopenia, and increases in liver function chemistry) were seen that required dosing to be discontinued. Upon resumption of dosing, these effects did not reappear. No histopathologic findings occurred in any multiple-dose toxicity study.

PEG-IFN is less immunogenic than IFN in mice. PEG-IFN and IFN were comparably immunogenic in monkeys. As a consequence of an immunogenic response to PEG-IFN by monkeys, which results in a marked reduction in serum exposure to PEG-IFN, a resolution of adverse effects was observed during the treatment period in all multiple-dose studies. The immunogenic response of monkeys to PEG-IFN was expected, as human interferons are known to be immunogenic in other animal species. Effects of treatment beyond 4 weeks could not be accurately assessed in the animal models as a result of their immunogenic response.

Despite the marked reduction in serum exposure with time, the exposure in animals (AUC, C_{max}) remained considerably higher than that seen in patients.

During all toxicity studies, a mild subcutaneous inflammatory reaction occurred at the injection sites of both PEG-IFN and placebo-control animals. No histopathological findings are observed in any of the multiple-dose toxicity studies, with the exception of subcutaneous inflammation at the injection sites.

Carcinogenesis: Peginterferon alfa-2a has not been tested for its carcinogenic potential.

Mutagenesis: Peginterferon alfa-2a was neither mutagenic nor clastogenic when tested in the Ames bacterial mutagenicity assay and in the in vitro chromosomal aberration assay in human lymphocytes, either in the presence or absence of metabolic activation.

Impairment of Fertility: As with other alpha interferons, prolongation of the menstrual cycle accompanied by both a decrease and delay in the peak of 17ß-estradiol and progesterone levels have been observed following administration of peginterferon alfa-2a to female cynomolgus monkeys. A return to normal menstrual rhythm followed discontinuation of treatment. Similar effects in the monkey have previously been associated with the occurrence of spontaneous abortions in addition to impaired female fertility. Peginterferon alfa-2a has not been studied for its effect on male fertility. However, treatment with interferon alfa-2a did not affect fertility of male rhesus monkeys treated for 5 months at doses up to 25 x 10^6 IU/kg/day.

The toxicology studies performed with PEG-IFN are summarized in the tables provided on the following pages.

Table 12 Summary of Acute (Single-Dose) Toxicity Studies

Title	Species/ Strain	No./ Sex/ Dose	Dose (μg/kg)	Duration of Observations/ Route of Administration	Maximum Non-Lethal Dose	Target Organs/ Systems of Toxicity
Acute Study	Monkeys/ Cynomolgus	One	6750	14 days after final dosing Subcutaneous	> 6750 μg/kg (technical limit dose)	Clinical signs: piloerection in the male and unsteady gait in the female. Clinical Pathology: transient mild anemia and decrease in WBC. Elevated ALT and decrease in protein and albumin. Mild subcutaneous hemorrhage at one injection site
Acute Study	Monkeys/ Cynomolgus	One	0, 15, 70, 300	14 days after final dosing Intravenous	> 300 μg/kg	Adverse effects were limited to bruising at the injection sites and transient elevation of AST in one monkey at the high dose

Table 13 Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Monkeys: 4-Week Twice Weekly Subcutaneous Dosing Study

Species/ Strain & No. Animals	Dose (µg/kg dose)	Day Sampled	Dose sampled	Mean [Serum] (ng/mL)	Mean C_{max} ±SD (ng/mL)	Mean $AUC_{0\text{-}72h}$ (ng·h/mL)	Treatment-Related Effects	Neutralizing Antibody Titer[b]
Monkeys Cynomolgus	15	1	1		98 ±21	6000	No toxicity was observed. Total antibodies to IFN were present in 1 female on day 15 and in all monkeys at the end of the study.	Median: 22.5
		15	4[a]	46				
3/sex/group		26	8		184 ±320	9770		Range: 17.5-400
	187.5	1	1		2050 ±263	130000	After 2 weeks of treatment, transient changes included: ↓mean protein (albumin, globulin fractions) and calcium level compared to pre-study. ↑ ALT in 2 males and AST in 1 male. No histopathologic findings were noted. Total antibodies to IFN were present in 1 male and 2 females on day 15 and in all monkeys at the end of the study.	Median: 60
		5	4[a]	1818				
		26	8		203 ±178	13200		Range: 30-400
	562.5	1	1		6565 ±1403	392000	Transient changes noted included: ↓ mean platelets prior to doses 3 and 5 in 1 male and 1 female; ↓ in WBC and neutrophil prior to dose 3; ↓mean protein and calcium prior to dose 5; ↑ ALT and AST in 1 male and 1 female, and ↑ absolute and relative liver and spleen weights. No histopathologic findings were noted. Total antibodies to IFN were present in all monkeys on day 15 and at the end of the study.	Median: 280
		15	4[a]	113				
		26	8		328 ±169	22400		Range: 60-560

[a] Samples 72 hours after dose 4 only.
[b] Samples 72 hours after last dose (dose 8). Neutralizing antibody titer is the reciprocal of the last dilution of serum that reduces the effective concentration of IFN alfa-2a from 10 U/mL to 1 U/mL.

Table 14 Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Monkeys: 4-Week Daily Subcutaneous Study with 4-Week Recovery Period

Species/ Strain No. Animals	Dose (µg/kg/ day)	Dose sampled (day)	Mean[a] [Serum] (ng/mL)	Mean[b] C_{max} (ng/mL)	Mean[b] AUC_{0-24h} (ng·h/mL)	Treatment-Related Effects	Total Antibody Titer (IFN binding Units/mL)	Neutralizing Antibody Titer[b]
Monkeys Cynomolgus 5/sex/ group	15	1 2 4 8 9 11 16 18 23 25 29[c]	 133 419 1072 948 270 331 50 46 70	133 - - 1070	1970 - - 23700	Transient changes that peaked at days 8 and/or 15 included: ↓ mean platelets that were significant only in males; ↓ WBC (neutrophils); ↓ reticulocytes. ↑ APTT in some males and females. No histopathologic findings were noted.	Day 16 (Treatment) 1 of 10 monkeys = 1110 Day 29 (Treatment)[c] Median: 1632 Range: 0 - 8196 Day 16 (Recovery) Median: 795 Range: 580 - 2391 Day 29 (Recovery) Median: 753 Range: 0 - 1125	Day 16 (Recovery) Median: 298 Range: 75 to 520 Day 29 (Recovery) Median: 210 Range: 130 to 480
	100	1 2 4 8 9 11 16 18 23 25 29[c]	 1250 4776 8280 8693 778 390 251 169 199	1250 - - 9240	18800 - - 209000	Transient changes that peaked at days 8 and/or 15 included: ↓ mean platelets that were significant only in males; ↓ WBC (neutrophils); ↓ reticulocytes; ↓ fibrinogen in males. ↑ APTT in some males and females. ↓ total protein. No histopathologic findings were noted.	Day 16 (Treatment) Median: 573 Range: 0 - 2228 Day 29 (Treatment)[c] Median: 3880 Range: 0 - 20475 Day 16 (Recovery) Median: 2657 Range: 608 - 4050 Day 29 (Recovery) Median: 2069 Range: 0 - 3833	Day 16 (Recovery) Median: 800 Range: 640 to 960 Day 29 (Recovery) Median: 1880 Range: 1200 to 2560
	600	1 2 4 8 9 11 16 18 23 25 29[c]	 6674 21445 48270 37113 684 365 329 631 572	6670 48900	102000 1120000	Transient changes that peaked at days 8 and/or 15 included: ↓ mean platelets that was significant only in males; ↓ WBC (neutrophils); ↓ reticulocytes; ↓ fibrinogen in males; significant ↑ APTT. There was ↑ RDW on days 22 and at end of treatment period. At most time points minimal ↓ HCT, HGB, and RBC were seen in males. ↓ total protein. ↓ calcium and BUN in females. No histo-pathologic findings were noted.	Day 16 (Treatment) Median: 3678 Range: 0 – 9736 Day 29 (Treatment)[c] Median: 14031 Range: 486-54694 Day 16 (Recovery) Median: 9397 Range: 2601-18225 Day 29 (Recovery) Median: 5931 Range: 1145-11328	Day 16 (Recovery) Median: 1840 Range: 400-4267 Day 29 (Recovery) Median: 880 Range: 760 to 8320

[a] Mean serum concentrations from samples obtained on specified days, prior to dosing.
[b] C_{max} and AUC_{0-24hr} were calculated for sample days 1 and 8 of the treatment period.
[c] Sampled 24 hours after the last dose (dose 28).
[d] The neutralizing antibody titer is the reciprocal of the last dilution of serum that reduces the effective concentration of IFN alfa-2a from 20 units/mL to 1 unit/mL.

Table 15 Summary of Multiple-Dose Toxicity and Toxicokinetic Studies in Monkeys: 13-Week Twice Weekly Subcutaneous Study with 4-Week Recovery Period

Species/ Strain & No. Animals	Dose (μg/kg/dose)	Day Sampled	Dose sampled	Mean C_{max} (ng/mL)	Mean $AUC_{0\text{-}96h}$ (ng·h/mL)	Treatment-Related Effects	Day Sampled	Median Total Antibody Titer[a] (IBU/mL)		Median Neutralizing Antibody Titer[a,b]	
Monkeys Cynomolgus 5/sex/ group	15	0 - 14	1 - 5	161 110	11837 3679	Slight transient ↓ leukocytes, neutrophils, total protein & albumin. Slight hemorrhage and inflammation at injection sites	33 - 61	543 391	(154-972) (0-783)	80 800	(40-320) (0-800)
		28 - 56	9 - 17	86 196	7642 15182		92 - 103	428 426	(0-823) (225-528)	1600 2400	(0-6400) (1600-3200)
		84	25	426	36947		117	202	(144-323)	6400	(1600-12800)
	50	0 - 14	1 - 5	515 425	40643 23508	Slight transient ↓ platelets, leucocytes, neutrophils, total protein & albumin. Slight transient ↑fibrinogen. Slight hemorrhage and inflammation at injection sites	33 - 61	814 692	(367-1350) (204-1070)	200 1600	(80-800) (400-12800)
		28 - 56	9 - 17	114 455	9819 36135		92 - 103	740 535	(223-1330) (187-1270)	2400 6400	(1600-12800) (3200-12800)
		84	25	819	69168		117	245	(0-980)	9600	(1600-12800)
	150	0 - 14	1 - 5	1445 423	117626 36424	Slight transient ↓ platelets, leukocytes, neutrophils, prothrombin time, total protein & albumin. Slight transient ↑ APTT & fibrinogen. Slight transient ↑ ALT (2 animals), Slight hemorrhage and inflammation at injection sites	33 - 61	959 919	(702-1130) (663-1270)	180 2400	(0-3200) (100-12800)
		28 - 56	9 - 17	228 1284	17798 104849		92 - 103	1270 1010	(982-5010)	8000 6400	(200-12800) (1600-12800)
		84	25	2545	226566		117	664	(358-812)	12800	(3200-12800)

[a] Range of observed values appears in brackets
[b] The neutralizing antibody titers are reported as the reciprocal of the last dilution of antiserum that neutralizes IFN alfa-2a from 10 lab units/mL to 1 lab unit/mL.

Table 16 Summary of Pilot Study on the Effects of PEG-IFN on Sex Steroid Hormones in Female Monkeys

Species/ Strain No. of Animal	Dose (μg/kg/dose) Regimen	Duration/ Route of Administration	Treatment-Related Effects
Cynomolgus Monkeys 2 females/ group	100, 300, 600 3 times/week Roferon-A (positive control): 25 MIU/kg, daily	Subcutaneous administration over 1 menstrual cycle or maximum of 6 weeks Roferon-A (positive control): intramuscular	Low Dose: no adverse effects Mid Dose: prolonged menstrual cycle (1 of 2), with delayed peak of 17β-estradiol and progesterone levels. High Dose: menstruation not observed (amenorrhea) in one of 2 females, with delayed peak of 17β-estradiol and progesterone levels. Interferon alfa-2a: prolonged menstrual cycle (2 of 2), with delayed peak of 17β-estradiol and progesterone levels.

Table 17 Summary of Study on the Effects of PEG-IFN on Sex Steroid Hormones in Female Monkeys with a Recovery Period

Species/ Strain & No. Animals	Dose (μg/kg/ dose)	Duration/ Route/ Regimen	Dose sampled	Mean C_{max} ±SD (ng/mL)	Mean $AUC_{0\text{-}48h}$±SD (ng·h/mL)	Median Neutralizing Antibody Titer[b]	Treatment-Related Effects
Monkeys Cynomolgus 5 females/ group	Interferon alfa-2a: 25 MIU/kg/day	Daily IM administered over 1 menstrual cycle or maximum of 6 weeks. Recovery period of 1 menstrual cycle.				96 hr after last dose: Median: 2000 Range: 1000-32000 20 days after last dose: Median: 4000 Range: 1000-32000	Prolonged menstrual cycle (4 of 5 monkeys), with a decrease and a delay in the peak of 17β-estratidiol and progesterone levels. Changes were reversible. Mean cycle length[c]: Dosing period: 39.2 d Recovery period: 32.6 d
	100	3 time/week SC administration over 1 menstrual cycle or maximum of 6 weeks. Recovery period of 1 menstrual cycle.	1 4 7 Last Dose	1650±284 3540±743 1410±3020 2000±2280	53400±13800 159000±30200 43000±91100 98600±104000[a]	96 hr after last dose: Median: 1600 Range: 400-51200 20 days after last dose: Median: 3200 Range: 200-51200	Prolonged menstrual cycle (2 of 5 monkeys), with a decrease and a delay in the peak of 17β- estradiol and progesterone levels. Changes were reversible. Mean cycle length[c]: Dosing period: 41.0 d Recovery period: 31.2 d
	600	3 time/ week SC administration over 1 menstrual cycle or maximum of 6 weeks. Recovery period of 1 menstrual cycle.	1 4 7 Last Dose	8870±2560 24400±7910 197±178 2050±1230	298000±79700 1060000±318000 5410±3190 138000±105000[a]	96 hr after last dose: Median: 6400 Range: 3200-12800 20 days after last dose: Median: 12800 Range: 3200- 12800	Prolonged menstrual cycle (5 of 5 monkeys), with a decrease and a delay in the peak of 17β- estradiol and progesterone levels. Changes were reversible. Mean cycle length[c]: Dosing period: 61.8 d Recovery period: 28.8 d

[a] Last dose values represent from mean $AUC_{0\text{-}96\ h.}$
[b] The neutralizing antibody titers are reported as the reciprocal of the last dilution of antiserum that neutralizes IFN alfa-2a from 10 lab units/mL to 1 lab unit/mL.
[c] Mean cycle length (Vehicle control): Dosing period:27.8 d; Recovery period:28.0 d

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PART III: CONSUMER INFORMATION
PrPEGASYS®
peginterferon alfa-2a

This leaflet is part III of a three-part "Product Monograph" published when PEGASYS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PEGASYS. Contact your doctor or pharmacist if you have any questions about the drug.

You have been prescribed PEGASYS (pronounced PEG-ah-sis) by your doctor to treat your Hepatitis C or Hepatitis B liver infection. Reading this information can help you learn about PEGASYS and how to make this medicine work best for you.

Before starting on this medication, please read this leaflet carefully and make sure that you have all supplies needed on hand. Please discuss the supplies you need with your doctor.

ABOUT THIS MEDICATION

What the medication is used for:
PEGASYS (peginterferon alfa-2a) is used for the treatment of chronic hepatitis C in:

- Adult patients without cirrhosis
- Adult patients with compensated cirrhosis,

including HCV/HIV co-infection patients with stable HIV disease with or without antiretroviral therapy.

PEGASYS is indicated for the treatment of both HBeAg-positive and HBeAg-negative chronic hepatitis B in:

- Patients with compensated liver disease, liver inflammation and evidence of viral replication (both cirrhotic and non-cirrhotic disease).

PEGASYS is not authorized for use in children and adolescents under the age of 18 years (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

What it does:
PEGASYS is a prescription medication belonging to the family of drugs called interferons. "Interferon" refers to a kind of protein normally made in a person's body. Interferons are a normal part of your body's defense system for fighting disease. Scientists can also make interferons outside of the body for use as medicines. Another name for PEGASYS is peginterferon alfa-2a. PEGASYS is a modified interferon that is different from the interferon made in a person's body. This modification helps the interferon (PEGASYS) stay in your body for a prolonged time and allows PEGASYS to be injected only once a week.

No one knows exactly how interferons work. However, treatment with PEGASYS increases your body's natural defense system for fighting disease.

What is Hepatitis C?
Hepatitis C is a liver disease caused by the hepatitis C virus. Hepatitis C is spread by contact with blood of a person carrying the hepatitis C virus.

Hepatitis C is more serious for some people than others. Most people who get hepatitis C carry the virus in their blood for the rest of their lives. Most of these people will have some liver damage, but many do not feel sick from the disease. In some people, the liver becomes badly damaged and scarred. This is called cirrhosis. Cirrhosis can cause the liver to stop working properly.

With PEGASYS therapy, the hepatitis C virus can be decreased to a level so low that it cannot be measured by blood tests. The virus is decreased and cannot be measured in 3 to 4 out of every 10 people who take PEGASYS therapy for approximately one year.

Your healthcare provider will monitor the effects of your medicine on your body through blood tests. While you are using PEGASYS, it is very important to get the blood tests your doctor orders. This will help your doctor see how well the medicine is working for you.

If you have any questions about your health conditions or PEGASYS, talk to your healthcare provider.

What is Hepatitis B?
Hepatitis B is a liver disease caused by the hepatitis B virus. Hepatitis B is spread by contact with blood and/or bodily fluids of a person carrying the hepatitis B virus.

Hepatitis B is more serious for some people than others. Most people who become infected never feel sick and recover completely; however, some people who get hepatitis B carry the virus in their blood for the rest of their lives even if they are symptom free. Some adults develop a chronic disease, which can lead to the liver being badly damaged and scarred (a condition called cirrhosis) and cancer of the liver later in life.

With PEGASYS treatment, you will have regular blood tests to help your healthcare provider check how the treatment is working and to check for side effects.

If you have questions about your health condition or PEGASYS, talk to your healthcare provider.

When it should not be used:

- you ever had an allergic reaction to other alpha interferons, or any of the ingredients in PEGASYS.
- you have autoimmune hepatitis (hepatitis caused by your immune system attacking your liver).
- you have unstable or advanced liver disease.
- you have an autoimmune disease (where the body's immune system attacks the body's own cells) such as psoriasis (a skin disease) or sarcoidosis.
- you are coinfected with HIV and you have unstable or advanced liver disease, as determined by your doctor.
- neonates and infants because the PEGASYS component contains benzyl alcohol. There have been rare reports of death in neonates and infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in neonates or infants is not known.
- you have a history of or current mental illness (such as depression or anxiety). PEGASYS therapy may make them worse. Tell your doctor if you are being treated or had treatment in the past for any mental problems, including depression, thoughts of ending your life (suicidal thoughts) or a feeling of loss of contact with reality, such as hearing voices or seeing things that are not there (psychosis). Tell your doctor if you take any medicines for these problems.
- you have problems with your thyroid gland.
- you are breast feeding.

What the medicinal ingredient is:
peginterferon alfa-2a

What the non-medicinal ingredients are:
acetic acid, benzyl alcohol, polysorbate 80, sodium acetate trihydrate, sodium chloride and water for injection

What dosage forms it comes in:
Pre-filled Syringes: Each syringe contains 180 mcg of PEGASYS in a 0.5 mL volume.
Vials: Each vial contains 180 mcg of PEGASYS in a 1 mL volume.
ProClick® Autoinjector: Each autoinjector contains 180 mcg of PEGASYS in a 0.5 mL volume.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Interferons, including PEGASYS cause or aggravate fatal or life-threatening neuropsychiatric (mental illness), autoimmune (where the body's immune system attacks the body's own cells), ischemic (conditions in which blood flow, and thus oxygen, is restricted to a part of the body) and infectious disorders. If you have persistently severe or worsening signs or symptoms of these conditions you should contact your doctor. Your doctor will assess you and may discontinue you from therapy. In many cases, but not all cases, these disorders resolve after stopping interferon therapy.

BEFORE you use PEGASYS talk to your doctor or pharmacist if:

- **you are pregnant or breast-feeding or are planning to become pregnant.**
- you have a history of or current mental illness (such as depression or anxiety).
- you have a history of drug or alcohol addiction or abuse.
- you have high blood pressure or a history of heart disease or previous heart attack or high blood fat (such as elevated triglyceride or cholesterol levels).
- you have a history of cancer.
- you have kidney problems.
- you have blood disorders, including anemia (low red blood cell count), thalassemia (Mediterranean anemia) and sickle-cell anemia
- you are taking any other medicines, including those not prescribed by your doctor. Your doctor should know if you are taking medicines called methadone or theophylline.
- you are taking the Chinese herbal medicine sho-saiko-to, also known as Xiao-Chai-Hu.
- you have had an organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system).
- you have diabetes (high blood sugar).
- you have problems with your thyroid gland.
- you have liver problems (other than hepatitis C or hepatitis B)
- you have lung (respiratory) problems, such as pneumonia, shortness of the breath, and Chronic Obstructive Pulmonary Disease (COPD).

This information will help your doctor and you decide whether you should use PEGASYS and what extra care may need to be taken while you are on these medicine. If you have any doubts about your health condition or about taking PEGASYS, talk to your doctor.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with PEGASYS include: methadone, sho-saiko-to/Xiao-Chai-Hu and theophylline.

Tell your doctor or pharmacist if you are taking Sebivo® (telbivudine) for chronic hepatitis B because taking this medicine together with PEGASYS may increase your risk of developing peripheral neuropathy (numbness, weakness, tingling, and/or burning sensations, or pain in the arms and/or legs). The combined use of these medications is not recommended.

PROPER USE OF THIS MEDICATION

Usual dose:

How should you take PEGASYS?
Your doctor has prescribed PEGASYS after carefully studying your case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours. Do not give your PEGASYS to anyone else.

PEGASYS is given as an injection just under the skin, on the stomach or thighs. You may hear people call this type of injection a "subcutaneous" or "Sub Q" injection. This means that the injection goes into the layer of fat just under the skin. If you have any questions about how to take PEGASYS or have trouble giving yourself the injections, call your doctor immediately.

Your healthcare provider will tell you how much medicine to take and how often to take it. PEGASYS is a ready-to-use solution usually given as a single injection once per week. Make sure that you drink plenty of fluids while you are being treated with PEGASYS.

PEGASYS is supplied in three different ways: pre-filled syringes, autoinjectors, and vials. It is important that you follow the **specific** instructions for using the kind of PEGASYS that your doctor has prescribed. **Whether you give yourself the injection, or another person gives the injection to you, it is important to follow the instructions (see Appendix 1 - How to use) in this information sheet.**

How long will you have to take PEGASYS?
Your doctor will tell you how long you need to use PEGASYS. Over time, your doctor may change your dose of PEGASYS. For information on how to change your dose of PEGASYS, see the section called **"How do you use PEGASYS?"** Only change your dose of PEGASYS if your doctor tells you to change it.

After 3 months of therapy, your doctor may ask you to have a blood test to determine how you are responding to your treatment.

What should you do if your doctor changes your dose of PEGASYS?
If your doctor changes your dose of PEGASYS, you will need to pull a different amount of medicine into the syringe from the vial. Your doctor will tell you which mark on the syringe to use. Do not change your dose of PEGASYS unless your doctor tells you to.

If you ever switch between using pre-filled syringes, autoinjectors, and vials, talk to your healthcare provider about how much PEGASYS to use. Equal volumes of liquid from the pre-filled syringes, autoinjectors, and the vials DO NOT contain the same amount of PEGASYS. If you switch between pre-filled syringes and vials, you will have to adjust the volume of liquid that you use to give your injection. If you do not adjust this, you could accidentally take too much or too little of your medicine.

The autoinjector is designed to deliver the full content. If your required dose is not available in an autoinjector, pre-filled syringes or vials should be used.

Are all interferons the same?
Once you start treatment with PEGASYS, do not switch to another brand of interferon and/or ribavirin without talking to your doctor. Other brands may not have the same effect on the treatment of your disease. Switching brands will also require a change in your dose.

Overdose:
If you take more than the prescribed amount of PEGASYS, call your doctor right away. Your doctor may want to examine you and take blood for testing.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of PEGASYS and remember **within 2 days** of the scheduled dose, give yourself an injection of PEGASYS as soon as you remember. Take your next PEGASYS dose on the day you would usually take it. If **more than 2 days have passed**, ask your doctor what you should do.

To get the most benefit from this medicine, it is important to take PEGASYS exactly as your doctor and healthcare providers tell you.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. PEGASYS can cause some serious side effects. Before starting PEGASYS, you should talk with your doctor about the possible benefits and possible side effects of treatment. Talk to your doctor or pharmacist if you are worried about side effects or find them very bothersome. There may be a way to relieve your symptoms. While taking PEGASYS, you will need to see your doctor regularly for medical examinations and blood tests to make sure your treatment is working and to check for side effects.
The most common side effects of interferon therapy, including PEGASYS are:

- Flu-like symptoms such as unusual tiredness, fever, chills, muscle aches, joint pain, and headaches. Most people have mild to moderate flu-like symptoms, but these usually decrease after the first few weeks of treatment. Taking acetaminophen (e.g. Tylenol®) or ibuprofen (e.g. Advil®) before you take PEGASYS can help with these symptoms. Ask your pharmacist or doctor for a recommendation as to which pain reliever to take. You can also try taking PEGASYS at night. You may be able to sleep through the symptoms.

Other common side effects can occur with PEGASYS, but are usually mild. These may include:

- Upset stomach, nausea, vomiting, loss of appetite, diarrhea, back pain, trouble sleeping, poor concentration, dizziness, decreased sexual desire, numbness or tingling, rash, dry itchy skin, hair thinning, redness and swelling at the injection site, problems with blood sugar, feeling tired and cough.

The serious possible side effects of interferon therapy, including PEGASYS are:

- Mood or behavioral problems including irritability (getting easily upset), depression (feeling low, feeling bad about yourself or feeling hopeless), and anxiety. Some patients may have aggressive behaviour (sometimes directed towards others) or develop thoughts about ending their lives (suicidal thoughts) and may attempt to do so. A few patients have ended their lives.
- Blood related disorders such as pancytopenia (marked decreases in red and white blood cells and platelets) and different forms of anemia
- A drop in the number of white blood cells causing a risk for infection, and drop in platelets resulting in bleeding if the numbers drop too low.
- Serious infections (bacterial, viral or fungal).
- Lung problems, such as difficulty breathing, pneumonia, or high blood pressure of the lungs (pulmonary hypertension).
- Eye problems that may cause blurred vision, a visual field deficit, or loss of vision.
- Autoimmune problems (where the body's own immune system begins to attack itself) including psoriasis or thyroid problems.
- Chest pain and very rarely heart attack.
- If you have chronic hepatitis B: A rise in a blood test that measures your liver function.
- Stroke: some patients may have weakness, loss of coordination and numbness
- Nerve problems: some patients may have numbness, tingling or burning sensation in the arms or legs
- Effect on growth in children: In a clinical study, it was observed that children can experience a delay in weight gain and height increase while being treated with PEGASYS and another drug called COPEGUS. Catch-up in growth happens after treatment stops, however some children may not reach the height that they were expected to have before treatment. (PEGASYS is not authorized for use in children and adolescents under the age of 18 years.)

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Less Common	Depressed or think of suicide		☑	
	Experience hallucinations, aggressiveness or confusion, or have trouble sleeping or concentrating		☑	
	Severe chest pain or irregular heart beat		☑	
	Trouble breathing or persistent cough		☑	
	A problem with your eyesight, a change in your vision (such as blurred vision, a visual field deficit or loss of vision), or hearing problem		☑	
	Unusual bleeding or bruising including severe nosebleeds		☑	
	Psoriasis (skin disease) and it gets worse while taking medicine		☑	
	Serious skin rash, hives, swelling or itching		☑	
	High fever or chills, or have pain when urinating		☑	
	Severe stomach pain or lower back pain		☑	
	Bloody diarrhea		☑	
	Woman and become pregnant		☑	
	Weakness, loss of coordination and numbness, tingling or burning sensation in the arms or legs		☑	

If you are concerned about these or any other unexpected effects while on PEGASYS, talk to your doctor or pharmacist.

HOW TO STORE IT

PEGASYS must be stored in the refrigerator at a temperature of 2-8°C. Do not freeze PEGASYS. Keeping PEGASYS at temperatures outside the recommended range can destroy the medicine.

Do not shake PEGASYS. Shaking can destroy PEGASYS so that it will not work.

Protect PEGASYS from light during storage.

Do not use after expiry date stated on the label.

Keep this and all other medicines out of the reach of children.

Appendix 1 How to Use

What is the safe way to handle and dispose of PEGASYS?
If you use PEGASYS at home, you must throw away syringes, autoinjectors, and needles in a box that will not let the needles stick through it. This will help protect you and other people from accidental needle sticks. Being stuck by a needle not only hurts, but also can pass diseases on to other people.

You can get these special boxes, often called "puncture-resistant containers," from your doctor or pharmacist. Keep this box out of the reach of children. When the box is full, follow your healthcare provider's instructions for throwing it away. Placing used boxes in the household waste should be avoided.

For safety reasons, always throw away syringes and needles promptly and never reuse them.

How do you use PEGASYS?
Please ask your doctor what supplies you need for properly administering this drug.

Pre filled Syringes:

The following instructions will help you learn how to use PEGASYS pre-filled syringes to inject yourself. It is important to follow these directions carefully. Talk to your healthcare provider if you have any concerns about how to use PEGASYS.

If you are giving this injection to someone else, a healthcare provider must teach you how to avoid needle sticks. Being stuck by a needle can pass diseases on to you.

Getting ready
Wash your hands carefully before handling any of the items.

Collect the necessary items before beginning:

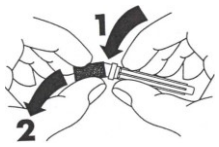
Included in the pack:
- a pre-filled syringe of PEGASYS
- an injection needle*

Not included in the pack:
- alcohol swabs
- small bandage or sterile gauze
- a puncture-resistant container for cleaning up when you are finished

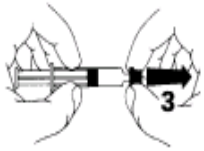
You may need to purchase these.

Preparing the syringe and needle for injection

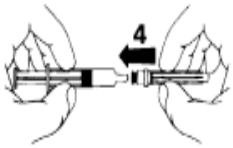
- Remove the protective cap that covers the back of the needle (1-2)



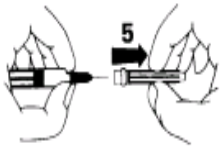
- Remove the rubber cap from the syringe (3). Do not touch the tip of the syringe.



- Place the needle firmly on the tip of the syringe (4).



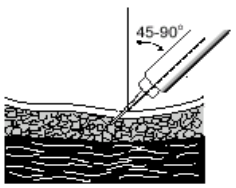
- Remove the needle guard from the syringe needle (5).



- To remove air bubbles from the syringe, hold the syringe with the needle pointing up. Tap the syringe gently to bring the bubbles to the top. Push the plunger up slowly to the correct dose. Replace the needle guard and place the syringe in a horizontal position until ready for use.
- Allow the solution to reach room temperature before injection or warm the syringe between your palms.
- Visually inspect the solution prior to administration. Do not use if it is discoloured (any colour besides colourless to light yellow) or if particles are present and report the lot number to your healthcare provider.
- You are now ready to inject the dose.

Injecting the solution

- Select the injection site in the abdomen or thigh (except your navel or waistline). Change your injection site each time.
- Clean and disinfect the skin where the injection is to be made with an alcohol swab.
- Wait for the area to dry.
- Remove the needle guard.
- With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil.
- Insert the needle all the way into the pinched skin at an angle of 45° to 90° (6).



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- Inject the solution by gently pushing the plunger all the way down.
- Pull the needle straight out of the skin.

Disposal of the injection materials

- Clean up after your injection
- Place the syringe and needle in a puncture-resistant container immediately after use.
- Throw away full containers according to directions provided by your healthcare provider.

Vials:

The following instructions will help you learn how to use PEGASYS vials to inject yourself. Please read all of these directions before trying to take your medicine. It is important to follow these directions carefully. Talk to your healthcare provider if you have any concerns about how to use PEGASYS.

If you are giving this injection to someone else, a healthcare provider must teach you how to avoid needle sticks. Being stuck by a needle can pass diseases on to you.

Getting ready

Wash your hands carefully before handling any of the items. Collect the necessary items before beginning.

Included in the pack:

- a vial of PEGASYS solution for injection.

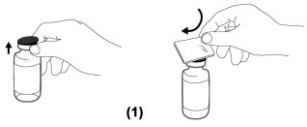
Not included in the pack:

- alcohol swabs
- 1 mL sterile syringe and needle (recommended: 27 gauge x ½ inch) for subcutaneous administration
- small bandage or sterile gauze
- a puncture-resistant container for cleaning up when you are finished.

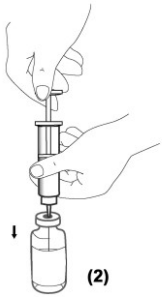
You may need to purchase these.

Measuring the dose of PEGASYS

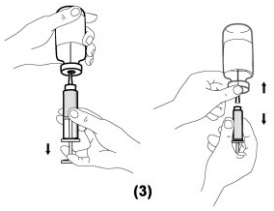
- Remove the protective cap from the PEGASYS vial (1).
- Clean the rubber top of the vial with an alcohol swab.



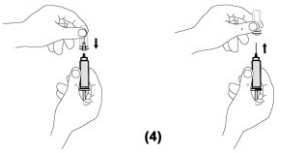
- Remove the needle and syringe from their packaging.
- Pull the syringe plunger back to the mark on the syringe barrel as instructed; this will pull air into the syringe barrel.
- Remove the needle guard without touching the needle and insert through the center of the stopper on the PEGASYS vial.
- Slowly inject all the air from the syringe into the air space above the solution. Do not inject air into the fluid (2).



- Hold the vial and syringe in one hand and turn the vial and the syringe upside down (3).
- With the syringe pointing up, make certain that the tip of the needle is in the PEGASYS solution. Your other hand will be free to move the plunger of the syringe.



- Slowly pull back on the plunger until the medicine is in the syringe up to the mark specified by your doctor.
- When you have pulled up the medicine to the right mark, pull the syringe needle out of the vial (4).

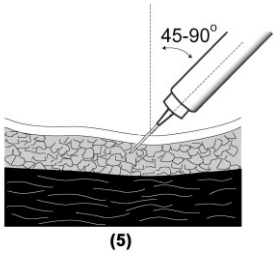


- Check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back. To remove air bubbles from the syringe, hold the syringe with the needle pointing up. Tap the syringe gently to bring the bubbles to the top. Push the plunger up slowly to the correct dose. Replace the needle guard and place the syringe in a horizontal position until ready for use.
- Allow the solution to reach room temperature before injection or warm the syringe between your palms.
- Visually inspect the solution prior to administration. Do not use if it is discoloured (any colour besides colourless to light yellow) or if particles are present and report the lot number to your healthcare provider.
- You are now ready to inject the dose.

Injecting the solution

- Select the injection site in the abdomen or thigh (except your navel or waistline). Change your injection site each time.
- Clean and disinfect the skin where the injection is to be made with an alcohol swab.
- Wait for the area to dry.
- Remove the needle guard.
- With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil.

- Insert the needle all the way into the pinched skin at an angle of 45° to 90° (5).



(5)

- Inject the solution by gently pushing the plunger all the way down.
- Pull the needle straight out of the skin.

Disposal of the injection materials
- Clean up after your injection.
- Place the syringe and needle in a puncture-resistant container immediately after use.
- Throw away full containers according to directions provided by your healthcare provider.

ProClick® Autoinjector:

The following instructions will help you or your caregiver learn how to use the PEGASYS ProClick® autoinjector correctly. These instructions do not replace training from your healthcare provider. Your healthcare provider should show you how to prepare and use your autoinjector properly before you use it for the first time. Ask your healthcare provider any questions you may have. Do not attempt to administer an injection until you are sure that you understand how to use the autoinjector.

The ready to use autoinjector includes a post-injection needle shield that was designed to help prevent needle-stick injuries and keeps the needle non-visible. The autoinjector is for single use only and is then to be discarded.

Do not:
- attempt to open the autoinjector or take it apart.
- expose to excessive forces or shock.
- use through clothing covering the skin.
- use if autoinjector appears to be damaged.
- use if medicine is cloudy, hazy, discoloured or has particles in it.
- shake the autoinjector.
- remove the blue cap if you are not ready to use it.
- re-use the autoinjector.
- push or pull the red needle-shield before, during or after use, as this is a safety device.

Getting ready:
Wash your hands carefully before handling any of the items.

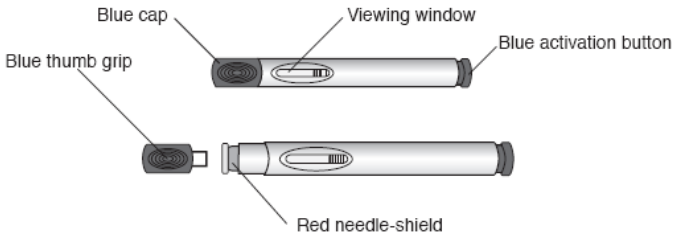
Collect the necessary items before beginning:

Included in the pack:
- a PEGASYS ProClick® autoinjector

Not included in the pack:
- alcohol swabs
- small bandage or sterile gauze
- a puncture-resistant container for cleaning up when you are finished

You may need to purchase these.

ProClick® Autoinjector parts:



How to proceed:

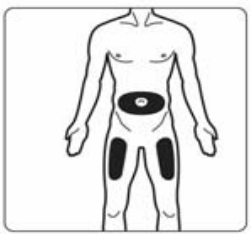
1. Visually check the autoinjector
Take the autoinjector out of the refrigerator. Visually examine the autoinjector, as well as the medicine through the viewing window. Do not shake. Do not remove the blue cap. If there is foam on the medicine, put the autoinjector back in the refrigerator and use at a later time.

Dispose of the autoinjector and use another if:
- the medicine is cloudy.
- the medicine contains particles.
- the medicine is any colour besides colourless to light yellow.
- any part of the autoinjector appears to be damaged.
- the expiration date has passed. You will find the expiration date on the box as well as on the label of the autoinjector itself.
- Contact your health care provider or pharmacist if the medicine in the autoinjector is cloudy or contains particles.

Keep the blue protective cap on the autoinjector until Step 4.

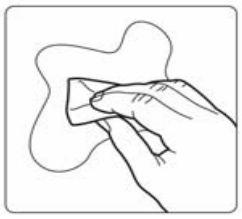
2. Allow the autoinjector to adjust to room temperature
Allow the refrigerated autoinjector to adjust to room temperature for about 20 minutes to warm up. Do not warm up autoinjector in any other way.

3. Choose and prepare an injection site
- Pick a place on your stomach or thigh (black areas in the picture). Avoid the 2 inch area around your belly-button (navel) and your waistline. You should use a different place each time you give yourself an injection. To minimize discomfort from injections, you may want to gently tap the area



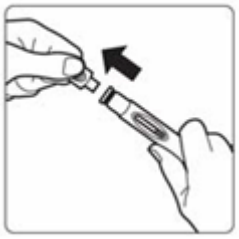
where you plan to give yourself an injection.

- Clean the injection site using an alcohol swab. Let the skin dry for 10 seconds. Be sure not to touch the cleaned area prior to injection.



4. Remove blue cap

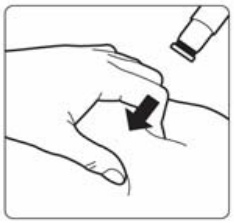
- Hold the autoinjector firmly with one hand and pull off the protective blue cap with the other hand.



NOTE: The cap contains a loose-fitting metal tube. Once the cap is removed, the autoinjector should be used immediately to avoid contamination. If it is not used within 5 minutes, the autoinjector should be disposed and a new autoinjector should be used. **Never re-attach the protective blue cap after removal.**

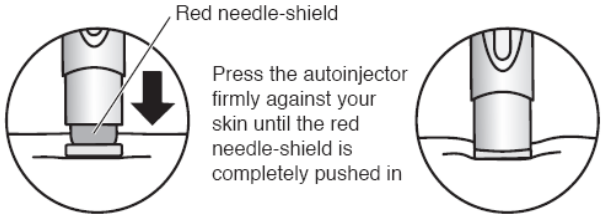
5. Place the autoinjector on the injection site

- Hold the autoinjector comfortably in your hand. Pinch and hold a fold of skin at the injection site with your free hand, such that the needle-shield can rest on the skin-fold firmly and safely.
- Place autoinjector straight up and down at a right angle (90°) on the injection site.



NOTE: Do not press the blue activation button yet.

- Press the autoinjector firmly against the skin until the red needle-shield is completely pushed in.
  - *The autoinjector is now unlocked and ready for injection.*



6. Give Injection

- While holding autoinjector firmly in place, press the blue activation button with your thumb and **immediately release the blue button. Make sure to take your thumb off the blue activation button and do not press it again.**
  - *You should hear a "click" sound, telling you that the injection has started.*
  - *The red indicator will move down in the viewing window during the injection.*

- Keep the autoinjector pressed firmly on the skin for **10 seconds** for injection to complete.
  - *You might hear a second click as the blue activation button pops back up.*
  - *The viewing window will now be completely red, confirming that the full dose has been delivered.*

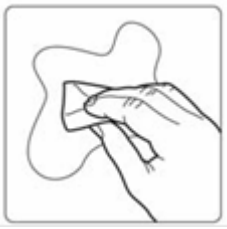
- Lift the autoinjector straight up (90° angle).
  - *The red needle-shield will automatically move out and lock to prevent needlestick injuries.*

CAUTION: If the viewing window is not completely filled by the red indicator:

- the needle-shield may not have locked.
  - Do not touch the tip of the autoinjector, since needlestick injuries may occur.
- you may not have received an entire dose.
  - Do not try to use the autoinjector again.
  - Do not repeat the injection with another autoinjector.
  - **Call your healthcare provider for instructions.**

7. After the injection

- Throw away used autoinjector and cap in a puncture-resistant disposable container immediately after use. Recapping is not required.
- Wipe the injection site with an alcohol swab.
- Wash your hands with soap and water.



- Throw away full containers according to directions provided by your healthcare provider.

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REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This brochure does not contain all known information about PEGASYS. If you have any further questions or concerns about your treatment with PEGASYS, please contact your doctor or pharmacist.

This document plus the full product monograph, prepared for health professionals can be found at:
. www.pharmaand.com. For questions or concerns, or to report adverse events or product complaints, please call 1 855 611-2724.
This leaflet was prepared by pharmaand GmbH, Taborstrasse 1, 1020 Vienna, Austria.

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*Injection needle manufactured by Terumo Europe N. V., Interleuvenlaan 40 Leuven, Belgium 3001. Ref: KN-2713RBR.