



PEGASYS®

(peginterferon alfa-2a)

Alpha interferons, including PEGASYS, may 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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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, but not all cases, these disorders resolve after stopping PEGASYS therapy (see WARNINGS and ADVERSE REACTIONS).

DESCRIPTION

PEGASYS, peginterferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Peginterferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

Each vial contains approximately 1.2 mL of solution to deliver 1.0 mL of drug product. Subcutaneous (SC) administration of 1.0 mL delivers 180 µg of drug product (expressed as the amount of interferon alfa-2a), 8.0 mg sodium chloride, 0.05 mg polysorbate 80, 10.0 mg benzyl alcohol, 2.62 mg sodium acetate trihydrate, and 0.05 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.01 .

CLINICAL PHARMACOLOGY

Pharmacodynamics

Interferons bind to specific receptors on the cell surface initiating intracellular signaling via a complex cascade of protein-protein interactions leading to 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.

Peginterferon alfa-2a stimulates the production of effector proteins such as serum neopterin and 2',5'-oligoadenylate synthetase, raises body temperature, and causes reversible decreases in leukocyte and platelet counts. The correlation between the in vitro and in vivo pharmacology and pharmacodynamic and clinical effects is unknown.

40 **Pharmacokinetics**

41 Maximal serum concentrations (C_{\max}) occur between 72 to 96 hours post dose,
42 and are sustained for up to 168 hours. The C_{\max} and AUC measurements of
43 PEGASYS increase in a dose-related manner. Week 48 mean trough
44 concentrations (16 ng/mL; range 4 to 28) are approximately 2-fold higher than
45 week 1 mean trough concentrations (8 ng/mL; range 0 to 15). Steady-state
46 serum levels are reached within 5 to 8 weeks of once weekly dosing. The peak
47 to trough ratio at week 48 is approximately 2.0.

48 The mean systemic clearance in healthy subjects given PEGASYS was 94
49 mL/h, which is approximately 100-fold lower than that for interferon alfa-2a
50 (ROFERON®-A). The mean terminal half-life after SC dosing in patients
51 with chronic hepatitis C was 80 hours (range 50 to 140 hours) compared to 5.1
52 hours (range 3.7 to 8.5 hours) for ROFERON-A.

53 PEGASYS administration yielded similar pharmacokinetics in male and
54 female healthy subjects. The AUC was increased from 1295 to 1663 ng·h/mL
55 in subjects older than 62 years taking 180 µg PEGASYS, but peak
56 concentrations were similar (9 vs 10 ng/mL) in those older and younger than
57 62 years.

58 In patients with end stage renal disease undergoing hemodialysis, there is a
59 25% to 45% reduction in clearance (see **PRECAUTIONS: Renal**
60 **Impairment**).

61 The pharmacokinetics of PEGASYS has not been adequately studied in
62 pediatric patients.

63 **CLINICAL STUDIES**

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

73 In study 1 (n=630), patients received either ROFERON-A (interferon alfa-2a)
74 3 MIU three times/week, PEGASYS 135 µg once each week, or PEGASYS
75 180 µg once each week. In study 2 (n=526), patients received either
76 ROFERON-A 6 MIU three times/week for 12 weeks followed by 3 MIU three
77 times/week for 36 weeks or PEGASYS 180 µg once each week.

78 In study 3 (n=269), patients received ROFERON-A 3 MIU three times/week,
79 PEGASYS 90 µg once each week, or PEGASYS 180 µg once each week.

Response to treatment was defined in the protocol as two consecutive undetectable HCV RNA values and normalization of ALT (alanine aminotransferase) at 24 weeks post-treatment (undetectable values must have occurred within 2 weeks of the scheduled visits at weeks 68 and 72 and must have been drawn at least 21 days apart). An exploratory analysis was also conducted in which response to treatment was defined as undetectable HCV RNA and normalization of ALT post-treatment (on or after study week 68). The results of the original and exploratory analysis are provided in Table 1.

In all three studies, treatment with PEGASYS 180 µg resulted in significantly more responding patients compared to treatment with ROFERON-A (see Table 1).

In study 1, response to PEGASYS 135 µg was not different from responses to 180 µg. In study 3, response rates with PEGASYS 90 µg were intermediate between PEGASYS 180 µg and ROFERON-A.

Table 1 Sustained Response at Week 72

	Study 1			Study 2			Study 3 (With Cirrhosis)		
	ROFERON-A 3 MIU (N=207)	PEGASYS 180 mg (N=208)	PEGASYS – ROFERON-A (95% CI)	ROFERON-A 6/3 MIU (N=261)	PEGASYS 180 mg (N=265)	PEGASYS – ROFERON-A (95% CI)	ROFERON-A 3 MIU (N=86)	PEGASYS 180 mg (N=87)	PEGASYS – ROFERON-A (95% CI)
Protocol:†									
Combined Virological and Biological Sustained Responder (wk 72)	9%	20%	11% (4%, 17%)	15%	28%	13% (6%, 20%)	3%	20%	16% (7%, 25%)
Sustained Virological Response*	9%	23%	13% (7%, 20%)	17%	31%	14% (7%, 22%)	5%	28%	23% (13%, 33%)
Exploratory:†									
Combined Virologic Response and Biological Sustained Responder (wk 72)	11%	24%	13% (6%, 20%)	17%	35%	18% (11%, 25%)	7%	23%	16% (6%, 26%)
Sustained Virological Response*	11%	26%	15% (8%, 23%)	19%	38%	19% (11%, 26%)	8%	30%	22% (11%, 33%)

*COBAS AMPLICOR® HCV Test, version 2.0, is a registered trademark of Roche Molecular Systems, Inc.

† See text for response definition.

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 µg therapy, either undetectable HCV RNA or at least a 2-log10 drop in HCV

103 RNA titer from baseline, 2% (3/156) achieved a sustained virological
104 response (see **DOSAGE AND ADMINISTRATION**).

105 Averaged over study 1, study 2, and study 3, response rates to PEGASYS
106 were 23% among patients with viral genotype 1 and 48% in patients with
107 other viral genotypes.

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

111 **INDICATIONS AND USAGE**

112 PEGASYS, peginterferon alfa-2a, is indicated for the treatment of adults with
113 chronic hepatitis C who have compensated liver disease and have not been
114 previously treated with interferon alfa. Patients in whom efficacy was
115 demonstrated included patients with compensated cirrhosis.

116 **CONTRAINDICATIONS**

117 PEGASYS is contraindicated in patients with:

- 118 • hypersensitivity to PEGASYS or any of its components
- 119 • autoimmune hepatitis
- 120 • decompensated hepatic disease prior to or during treatment with
121 PEGASYS

122
123 PEGASYS is also contraindicated in neonates and infants because it contains
124 benzyl alcohol. Benzyl alcohol has been reported to be associated with an
125 increased incidence of neurological and other complications in neonates and
126 infants which are sometimes fatal.

127 **WARNINGS**

128 **General**

129 Patients should be monitored for the following serious conditions, some of
130 which may become life threatening. Patients with persistently severe or
131 worsening signs or symptoms should have their therapy withdrawn (see
132 **BOXED WARNING**).

133 **Neuropsychiatric**

134 Life-threatening neuropsychiatric reactions may manifest in patients receiving
135 therapy with PEGASYS. Depression, suicidal ideation, and suicidal attempt
136 may occur in patients with and without previous psychiatric illness.

137 PEGASYS should be used with extreme caution in patients who report a
138 history of depression. Neuropsychiatric adverse events observed with alpha
139 interferon treatment include relapse of drug addiction, drug overdose,
140 aggressive behavior, psychoses, hallucinations, bipolar disorders and mania.

141 Physicians should monitor all patients for evidence of depression and other
142 psychiatric symptoms. Patients should be advised to report any sign or
143 symptom of depression or suicidal ideation to their prescribing physicians. In
144 severe cases, therapy should be stopped immediately and psychiatric
145 intervention instituted (see **ADVERSE REACTIONS** and **DOSAGE AND**
146 **ADMINISTRATION**).

147 **Bone Marrow Toxicity**

148 PEGASYS suppresses bone marrow function and may result in severe
149 cytopenias. Very rarely alpha interferons may be associated with aplastic
150 anemia. It is advised that complete blood counts (CBC) be obtained pre-
151 treatment and monitored routinely during therapy (see **PRECAUTIONS:**
152 **Laboratory Tests**).

153 PEGASYS should be used with caution in patients with baseline neutrophil
154 counts <1500 cells/mm³, with baseline platelet counts $<90,000$ cells/mm³ or
155 baseline hemoglobin <10 g/dL. PEGASYS therapy should be discontinued, at
156 least temporarily, in patients who develop severe decreases in neutrophil
157 and/or platelet counts (see **DOSAGE AND ADMINISTRATION: Dose**
158 **Modifications**).

159 **Cardiovascular Disorders**

160 Hypertension, supraventricular arrhythmias, chest pain, and myocardial
161 infarction have been observed in patients treated with PEGASYS.

162 PEGASYS should be administered with caution to patients with preexisting
163 cardiac disease.

164 **Hypersensitivity**

165 Severe acute hypersensitivity reactions (eg, urticaria, angioedema,
166 bronchoconstriction, anaphylaxis) have been rarely observed during alpha
167 interferon therapy. If such reaction occurs, therapy with PEGASYS should be
168 discontinued and appropriate medical therapy immediately instituted.

169 **Endocrine Disorders**

170 PEGASYS causes or aggravates hypothyroidism and hyperthyroidism.
171 Hyperglycemia, hypoglycemia, and diabetes mellitus have been observed to
172 develop in patients treated with PEGASYS. Patients with these conditions at
173 baseline who cannot be effectively treated by medication should not begin
174 PEGASYS therapy. Patients who develop these conditions during treatment
175 and cannot be controlled with medication may require discontinuation of
176 PEGASYS therapy.

177 **Autoimmune Disorders**

178 Development or exacerbation of autoimmune disorders including myositis,
179 hepatitis ITP, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis,

180 and systemic lupus erythematosus have been reported in patients receiving
181 alpha interferon. PEGASYS should be used with caution in patients with
182 autoimmune disorders.

183 **Pulmonary Disorders**

184 Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans,
185 interstitial pneumonitis and sarcoidosis, some resulting in respiratory failure
186 and/or patient deaths, may be induced or aggravated by PEGASYS or alpha
187 interferon therapy. Patients who develop persistent or unexplained pulmonary
188 infiltrates or pulmonary function impairment should discontinue treatment
189 with PEGASYS.

190 **Colitis**

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

197 **Pancreatitis**

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

202 **Ophthalmologic Disorders**

203 Decrease or loss of vision, retinopathy including macular edema, retinal artery
204 or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis,
205 and papilledema are induced or aggravated by treatment with PEGASYS or
206 other alpha interferons. All patients should receive an eye examination at
207 baseline. Patients with preexisting ophthalmologic disorders (eg, diabetic or
208 hypertensive retinopathy) should receive periodic ophthalmologic exams
209 during interferon alpha treatment. Any patient who develops ocular symptoms
210 should receive a prompt and complete eye examination. PEGASYS treatment
211 should be discontinued in patients who develop new or worsening
212 ophthalmologic disorders.

213 **PRECAUTIONS**

214 **General**

- 215 • The safety and efficacy of PEGASYS have not been established in
216 patients who have failed other alpha interferon treatments.
- 217 • The safety and efficacy of PEGASYS for the treatment of hepatitis C in
218 liver or other organ transplant recipients have not been established.

- 219 • The safety and efficacy of PEGASYS for the treatment of patients with
220 HCV co-infected with human immunodeficiency virus (HIV) or hepatitis
221 B virus (HBV) have not been established.

222 **Renal Impairment**

223 A 25% to 45% higher exposure to PEGASYS is seen in subjects undergoing
224 hemodialysis. In patients with impaired renal function, signs and symptoms of
225 interferon toxicity should be closely monitored. Doses of PEGASYS should
226 be adjusted accordingly. PEGASYS should be used with caution in patients
227 with creatinine clearance <50 mL/min (see **DOSAGE AND**
228 **ADMINISTRATION: Dose Modifications**).

229 **Information for Patients**

230 Patients receiving PEGASYS should be directed in its appropriate use,
231 informed of the benefits and risks associated with treatment, and referred to
232 the PEGASYS Medication Guide.

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

235 If home use is prescribed, a puncture-resistant container for the disposal of
236 used needles and syringes should be supplied to the patients. Patients should
237 be thoroughly instructed in the importance of proper disposal and cautioned
238 against any reuse of any needles and syringes. The full container should be
239 disposed of according to the directions provided by the physician (see
240 enclosed **MEDICATION GUIDE**).

241 **Laboratory Tests**

242 Before beginning PEGASYS therapy, standard hematological and
243 biochemical laboratory tests are recommended for all patients.

244 After initiation of therapy, hematological tests should be performed at 2 weeks
245 and biochemical tests should be performed at 4 weeks. Additional testing
246 should be performed periodically during therapy. In the clinical studies, the
247 CBC (including hemoglobin level and white blood cell [WBC] and platelet
248 counts) and chemistries (including liver function tests and uric acid) were
249 measured at 1, 2, 4, 6, and 8, and then every 4 weeks, or more frequently if
250 abnormalities were found. Thyroid stimulating hormone (TSH) was measured
251 every 12 weeks.

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

- 255 • Platelet count $\geq 90,000$ cells/mm³ (as low as 75,000 cells/mm³ in patients
256 with cirrhosis or transition to cirrhosis)
- 257 • Absolute neutrophil count (ANC) ≥ 1500 cells/mm³
- 258 • Serum creatinine concentration <1.5 x upper limit of normal

- TSH and T₄ within normal limits or adequately controlled thyroid function

PEGASYS treatment was associated with decreases in WBC, ANC and platelet counts often starting within the first 2 weeks of treatment (see **ADVERSE REACTIONS**). Dose reduction is recommended in patients with hematologic abnormalities (see **DOSAGE AND ADMINISTRATION: Dose Modifications**). In clinical trials with PEGASYS, the hematologic abnormalities were reversible upon dose reduction or cessation of therapy.

While fever may be associated with the flu-like syndrome reported commonly during PEGASYS therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia.

Transient elevations in ALT (2-fold to 5-fold above baseline) were observed in some patients receiving PEGASYS, including patients with virologic response. Transient elevations were not associated with deterioration of other liver function tests. However, 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: Dose Modifications**).

Drug Interactions

Treatment with PEGASYS once weekly for 4 weeks in healthy subjects was associated with an inhibition of P450 1A2 and a 25% increase in theophylline AUC. Theophylline serum levels should be monitored and appropriate dose adjustments considered for patients given both theophylline and PEGASYS (see **PRECAUTIONS**). There was no effect on the pharmacokinetics of representative drugs metabolized by CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

PEGASYS has not been tested for its carcinogenic potential.

Mutagenesis

PEGASYS did not cause DNA damage 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

PEGASYS may impair fertility. Prolonged menstrual cycles and/or amenorrhea were observed in female cynomolgus monkeys given SC injections of 600 µg/kg/dose (7200 µg/m²/dose) of PEGASYS every other day for one month, at approximately 180 times the recommended weekly human dose for a 60 kg person (based on body surface area). Menstrual cycle

irregularities were accompanied by both a decrease and delay in the peak 17 β -estradiol and progesterone levels following administration of PEGASYS to female monkeys. A return to normal menstrual rhythm followed cessation of treatment. Every other day dosing with 100 μ g/kg (1200 μ g/m²) PEGASYS (equivalent to approximately 30 times the recommended human dose) had no effects on cycle duration or reproductive hormone status.

The effects of PEGASYS on male fertility have not been studied. However, no adverse effects on fertility were observed in male Rhesus monkeys treated with non-pegylated interferon alfa-2a for 5 months at doses up to 25 x 10⁶ IU/kg/day.

Pregnancy

Pregnancy Category C

PEGASYS has not been studied for its teratogenic effect. Non-pegylated interferon alfa-2a treatment of pregnant Rhesus monkeys at approximately 20 to 500 times the human weekly dose resulted in a statistically significant increase in abortions. No teratogenic effects were seen in the offspring delivered at term. PEGASYS should be assumed to also have abortifacient potential. There are no adequate and well-controlled studies of PEGASYS in pregnant women. PEGASYS is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. PEGASYS is recommended for use in women of childbearing potential only when they are using effective contraception during therapy.

Nursing Mothers

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 must be made whether to discontinue nursing or discontinue the treatment.

Pediatric Use

The safety and effectiveness of PEGASYS in children below the age of 18 years have not been established.

PEGASYS contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal.

Geriatric Use

Clinical studies of PEGASYS did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Adverse reactions related to alpha interferons, such as CNS, cardiac, and systemic (eg, flu-like) effects may be more severe in the elderly and

337 caution should be exercised in the use of PEGASYS in this population. This
338 drug is known to be excreted by the kidney, and the risk of toxic reactions to
339 this drug may be greater in patients with impaired renal function. Because
340 elderly patients are more likely to have decreased renal function, care should
341 be taken in dose selection and it may be useful to monitor renal function.

342 **ADVERSE REACTIONS**

343 PEGASYS causes a broad variety of serious adverse reactions (see **BOXED**
344 **WARNING** and **WARNINGS**). In all studies, one or more serious adverse
345 reactions occurred in 9% of patients receiving PEGASYS. Nearly all patients
346 in clinical trials experienced one or more adverse events. The most commonly
347 reported adverse reactions were psychiatric reactions, including depression,
348 irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia,
349 headache and rigors. The most common reason for dose modification or
350 withdrawal from studies was hematologic abnormalities.

351 Because clinical trials are conducted under widely varying and controlled
352 conditions, adverse reaction rates observed in clinical trials of a drug cannot
353 be directly compared to rates in the clinical trials of another drug. Also, the
354 adverse event rates listed here may not predict the rates observed in a broader
355 patient population in clinical practice. More than 1000 patients have been
356 treated with PEGASYS in clinical trials. Table 2 shows those adverse
357 reactions occurring in $\geq 5\%$ of patients receiving PEGASYS 180 μg (n=559)
358 in clinical trials. The population encompassed an age range of 18 to 76.
359 Seventy percent of the patients were male and 86% were Caucasian.

360 **Table 2** **Adverse Reactions Occurring in [≥]5% of Patients in**
361 **Hepatitis C Clinical Trials (Pooled Studies 1, 2,**
362 **and 3)**

Body System/Adverse Events	PEGASYS 180mg N = 559 (%)	ROFERON-A* N = 554 (%)
Gastrointestinal		
Nausea	23	30
Diarrhea	16	16
Abdominal pain	15	15
Nausea and vomiting	5	8
Dry mouth	6	3
General		
Fatigue	50	50
Pyrexia	36	41
Rigors	32	42
Injection-site reaction	22	18
Pain	11	12
Asthenia	5	6
Hematologic		
Neutropenia	21	8
Thrombocytopenia	5	2
Metabolism and Nutrition		
Anorexia	17	17
Musculoskeletal, Connective Tissue and Bone		
Myalgia	37	38
Arthralgia	28	29
Back pain	9	10
Neurological		
Headache	54	58
Insomnia	19	23
Dizziness	16	12
Concentration impairment	8	10
Memory impairment	5	4
Psychiatric		
Depression	18	19
Irritability	13	17
Anxiety	6	5
Depressed mood	1	5

Body System/Adverse Events	PEGASYS 180mg N = 559 (%)	ROFERON-A* N = 554 (%)
Skin and Subcutaneous Tissue		
Alopecia	23	30
Pruritus	12	8
Sweating increased	6	7
Dermatitis	8	3
Rash	5	4

363 *Either 3 MIU or 6/3 MIU of ROFERON-A.

364 Serious adverse events included the following: substance overdose, hepatic
365 dysfunction, fatty liver, cholangitis, arrhythmia, suicidal ideation, suicide,
366 diabetes mellitus, autoimmune phenomena, peripheral neuropathy, peptic
367 ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer,
368 endocarditis, pneumonia, interstitial pneumonitis, pulmonary embolism,
369 coma, myositis, and cerebral hemorrhage. Each of the above individual events
370 occurred at a frequency of $\leq 1\%$.

371 **Laboratory Test Values**

372 **Hematology**

373 Treatment with PEGASYS 180 μg was associated with decreases in total
374 WBC, ANC and platelet counts, which generally improved with dosage
375 modification and returned to pre-treatment levels within 4 to 8 weeks upon
376 cessation of therapy (see **PRECAUTIONS** and **DOSAGE AND**
377 **ADMINISTRATION**). Approximately 4% of patients had transient decreases
378 in ANC to levels below 500 cells/mm³ at some time during therapy.
379 PEGASYS treatment was also associated with decreases in values for platelet
380 counts. Approximately 5% of patients had decreases in platelet counts to
381 levels below 50,000 cells/mm³.

382 Although treatment with PEGASYS 180 μg was associated with small gradual
383 decreases in hemoglobin and hematocrit, less than 1% of all patients,
384 including those with cirrhosis, required dose modification for anemia.

385 **Thyroid Function**

386 PEGASYS treatment was associated with the development of abnormalities in
387 thyroid laboratory values, some with associated clinical manifestations. The
388 rates of clinically relevant hypothyroidism or hyperthyroidism (requiring
389 treatment, dose modification or discontinuation) were 4% and 1%,
390 respectively. Among the patients who developed new onset thyroid
391 abnormalities during PEGASYS treatment, approximately half still had
392 abnormalities during the follow-up period (see **PRECAUTIONS:**
393 **Laboratory Tests**).

394 Immunogenicity

395 Two percent of patients (8/409) receiving PEGASYS developed low-titer
396 neutralizing antibodies (using an assay of a sensitivity of 100 INU/mL). Six
397 percent (24/409) of patients treated with PEGASYS developed binding
398 antibodies to interferon alfa-2a, as assessed by an ELISA assay.

399 The clinical and pathological significance of the appearance of serum
400 neutralizing antibodies is unknown. No apparent correlation of antibody
401 development to clinical response or adverse events was observed. The
402 percentage of patients whose test results were considered positive for
403 antibodies is highly dependent on the sensitivity and specificity of the assays.

404 Additionally the observed incidence of antibody positivity in these assays may
405 be influenced by several factors including sample timing and handling,
406 concomitant medications, and underlying disease. For these reasons,
407 comparison of the incidence of antibodies to PEGASYS with the incidence of
408 antibodies to these products may be misleading.

409 OVERDOSAGE

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

417 DOSAGE AND ADMINISTRATION

418 The recommended dose of PEGASYS is 180 µg (1.0 mL) once weekly for 48
419 weeks by subcutaneous administration in the abdomen or thigh.

420 There are no safety and efficacy data on treatment for longer than 48 weeks.
421 Consideration should be given to discontinuing therapy after week 12
422 virological results are available if the patient has failed to demonstrate a
423 response (see **CLINICAL STUDIES**).

424 A patient should self-inject PEGASYS only if the physician determines that it
425 is appropriate and the patient agrees to medical follow-up as necessary and
426 training in proper injection technique has been provided to him/her (see
427 illustrated **MEDICATION GUIDE** for instructions).

428 PEGASYS should be inspected visually for particulate matter and
429 discoloration before administration, and not used if particulate matter is
430 visible or product is discolored. Vials with particulate matter or discoloration
431 should be returned to the pharmacist.

432 **Dose Modifications**

433 **General**

434 When dose modification is required for moderate to severe adverse reactions
435 (clinical and/or laboratory), initial dose reduction to 135 µg (0.75 mL) is
436 generally adequate. However, in some cases, dose reduction to 90 µg (0.5 mL)
437 may be needed. Following improvement of the adverse reaction, re-escalation
438 of the dose may be considered (see **WARNINGS, PRECAUTIONS, and**
439 **ADVERSE REACTIONS**).

440 **Hematological**

441 Dose reduction to 135 µg PEGASYS is recommended if the neutrophil count
442 is less than 750 cells/mm³. For patients with ANC values below 500
443 cells/mm³, treatment should be suspended until ANC values return to more
444 than 1000 cells/mm³. Therapy should initially be reinstituted at 90 µg
445 PEGASYS, and the neutrophil count monitored.

446 Dose reduction to 90 µg PEGASYS is recommended if the platelet count is
447 less than 50,000 cells/mm³. Cessation of therapy is recommended when
448 platelet count is below 25,000 cells/mm³.

449 **Renal Function**

450 In patients with end-stage renal disease requiring hemodialysis, dose reduction
451 to 135 µg PEGASYS is recommended. Signs and symptoms of interferon
452 toxicity should be closely monitored.

453 **Liver Function**

454 In patients with progressive ALT increases above baseline values, the dose of
455 PEGASYS should be reduced to 90 µg. If ALT increases are progressive
456 despite dose reduction or accompanied by increased bilirubin or evidence of
457 hepatic decompensation, therapy should be immediately discontinued.

458 **HOW SUPPLIED**

459 **Single Dose Vial**

460 Each PEGASYS (peginterferon alfa-2a) 180 µg single use, clear glass vial
461 provides 1.0 mL containing 180 µg peginterferon alfa-2a for SC injection.
462 Each package contains 1 vial (NDC 0004-0350-09).

463 **Storage**

464 Store in the refrigerator at 36° to 46°F (2° to 8°C). Do not freeze or shake.
465 Protect from light. Vials are for single use only. Discard any unused portion.

466 Rx only



Pharmaceuticals

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