

**PEGASYS****(peginterferon alfa-2a)****Rx only**

Alpha interferons, including PEGASYS (peginterferon alfa-2a), 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. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping PEGASYS therapy (see WARNINGS and ADVERSE REACTIONS).

Use with Ribavirin. Ribavirin, including COPEGUS , may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen (see COPEGUS Package Insert for additional information and other WARNINGS).

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*.

PEGASYS is supplied as an injectable solution in vials and prefilled syringes.

180 µg/1.0 mL Vial: A 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 ± 0.5 .

180 µg/0.5 mL Prefilled Syringe: Each syringe contains 0.6 mL of solution to deliver 0.5 mL of drug product. Subcutaneous (sc) administration of 0.5 mL delivers 180 µg of drug product (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, and 0.0231 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.5 .

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40 CLINICAL PHARMACOLOGY

41 Pharmacodynamics

42 Interferons bind to specific receptors on the cell surface initiating intracellular signaling
43 via a complex cascade of protein-protein interactions leading to rapid activation of gene
44 transcription. Interferon-stimulated genes modulate many biological effects including the
45 inhibition of viral replication in infected cells, inhibition of cell proliferation and
46 immunomodulation. The clinical relevance of these in vitro activities is not known.

47 PEGASYS stimulates the production of effector proteins such as serum neopterin and 2',
48 5'-oligoadenylate synthetase.

49 Pharmacokinetics

50 Maximal serum concentrations (C_{max}) and AUC increased in a nonlinear dose related
51 manner following administration of 90 to 270 μg of PEGASYS. Maximal serum
52 concentrations (C_{max}) occur between 72 to 96 hours post-dose.

53 Week 48 mean trough concentrations (16 ng/mL; range 4 to 28) at 168 hours post-dose
54 are approximately 2-fold higher than week 1 mean trough concentrations (9 ng/mL; range
55 0 to 15). Steady-state serum levels are reached within 5 to 8 weeks of once weekly
56 dosing. The peak to trough ratio at week 48 is approximately 2. The mean systemic
57 clearance in healthy subjects given PEGASYS was 94 mL/h, which is approximately
58 100-fold lower than that for interferon alfa-2a (ROFERON -A). The mean terminal half-
59 life after sc dosing in patients with chronic hepatitis C was 80 hours (range 50 to 140
60 hours) compared to 5 hours (range 3.7 to 8.5 hours) for ROFERON-A.

61 Special Populations

62 Gender and Age

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

67 Pediatric Patients

68 In a population pharmacokinetics study, 14 children 2 to 8 years of age with CHC
69 received PEGASYS based on their body surface area (BSA of the child \times
70 180 $\mu\text{g}/1.73\text{m}^2$). The clearance of PEGASYS in children was nearly 4-fold lower
71 compared to the clearance reported in adults.

72 Steady-state trough levels in children with the BSA-adjusted dosing were similar to
73 trough levels observed in adults with 180 μg fixed dosing. Time to reach the steady state
74 in children is approximately 12 weeks, whereas in adults, steady state is reached within 5
75 to 8 weeks. In these children receiving the BSA adjusted dose, the mean exposure (AUC)
76 during the dosing interval is predicted to be 25% to 70% higher than that observed in
77 adults receiving 180 μg fixed dosing. The safety and effectiveness of PEGASYS in
78 patients below the age of 18 years have not been established (see **PRECAUTIONS:**
79 **Pediatric Use**).

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80 Renal Dysfunction

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

83 The pharmacokinetics of ribavirin following administration of COPEGUS have not been
84 studied in patients with renal impairment and there are limited data from clinical trials on
85 administration of COPEGUS in patients with creatinine clearance <50 mL/min.
86 Therefore, patients with creatinine clearance <50 mL/min should not be treated with
87 COPEGUS (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

88 Effect of Food on Absorption of Ribavirin

89 Bioavailability of a single oral dose of ribavirin was increased by co-administration with
90 a high-fat meal. The absorption was slowed (T_{max} was doubled) and the AUC_{0-192h} and
91 C_{max} increased by 42% and 66%, respectively, when COPEGUS was taken with a high-
92 fat meal compared with fasting conditions (see **DOSAGE AND ADMINISTRATION**).

93 Drug Interactions

94 Nucleoside Analogues

95 In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and
96 zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular
97 triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of
98 HIV/HCV virologic suppression) interaction was observed when ribavirin and
99 lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were co-administered as part
100 of a multi-drug regimen to HCV/HIV coinfecting patients (see **PRECAUTIONS: Drug**
101 **Interactions**).

102 In vitro, didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is
103 increased when didanosine is co-administered with ribavirin (see **PRECAUTIONS:**
104 **Drug Interactions**).

105 Drugs Metabolized by Cytochrome P450

106 There was no effect on the pharmacokinetics of representative drugs metabolized by CYP
107 2C9, CYP 2C19, CYP 2D6 or CYP 3A4.

108 Treatment with PEGASYS once weekly for 4 weeks in healthy subjects was associated
109 with an inhibition of P450 1A2 and a 25% increase in theophylline AUC (see
110 **PRECAUTIONS: Drug Interactions**).

111 Methadone

112 The pharmacokinetics of concomitant administration of methadone and PEGASYS were
113 evaluated in 24 PEGASYS naive chronic hepatitis C (CHC) patients (15 male, 9 female)
114 who received 180 µg PEGASYS subcutaneously weekly. All patients were on stable
115 methadone maintenance therapy (median dose 95 mg, range 30 mg to 150 mg) prior to
116 receiving PEGASYS. Mean methadone PK parameters were 10% to 15% higher after 4
117 weeks of PEGASYS treatment as compared to baseline (see **PRECAUTIONS: Drug**

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118 **Interactions**). Methadone did not significantly alter the PK of PEGASYS as compared to
119 a PK study of 6 chronic hepatitis C patients not receiving methadone.

120 **CLINICAL STUDIES**

121 **Chronic Hepatitis C Studies 1, 2, and 3: PEGASYS Monotherapy**

122 The safety and effectiveness of PEGASYS for the treatment of hepatitis C virus infection
123 were assessed in three randomized, open-label, active-controlled clinical studies. All
124 patients were adults, had compensated liver disease, detectable hepatitis C virus (HCV),
125 liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon.
126 All patients received therapy by sc injection for 48 weeks, and were followed for an
127 additional 24 weeks to assess the durability of response. In studies 1 and 2, approximately
128 20% of subjects had cirrhosis or bridging fibrosis. Study 3 enrolled patients with a
129 histological diagnosis of cirrhosis (78%) or bridging fibrosis (22%).

130 In Study 1 (n=630), patients received either ROFERON-A (interferon alfa-2a) 3 MIU
131 three times/week (tiw), PEGASYS 135 µg once each week (qw) or PEGASYS 180 µg
132 qw. In Study 2 (n=526), patients received either ROFERON-A 6 MIU tiw for 12 weeks
133 followed by 3 MIU tiw for 36 weeks or PEGASYS 180 µg qw. In Study 3 (n=269),
134 patients received ROFERON-A 3 MIU tiw, PEGASYS 90 µg qw or PEGASYS 180 µg
135 once each week.

136 In all three studies, treatment with PEGASYS 180 µg resulted in significantly more
137 patients who experienced a sustained response (defined as undetectable HCV RNA [<50
138 IU/mL] using the COBAS AMPLICOR HCV Test, version 2.0 and normalization of
139 ALT on or after study week 68) compared to treatment with ROFERON-A. In Study 1,
140 response to PEGASYS 135 µg was not different from response to 180 µg. In Study 3,
141 response to PEGASYS 90 µg was intermediate between PEGASYS 180 µg and
142 ROFERON-A.

143 **Table 1 Sustained Response to Monotherapy Treatment**

	Study 1			Study 2			Study 3		
	ROFERON-A 3 MIU (N=207)	PEGASYS 180 µg (N=208)	DIFF* (95% CI)	ROFERON-A 6/3 MIU (N=261)	PEGASYS 180 µg (N=265)	DIFF* (95% CI)	ROFERON-A 3 MIU (N=86)	PEGASYS 180 µg (N=87)	DIFF* (95% CI)
Combined Virologic and Biologic Sustained Response	11%	24%	13 (6, 20)	17%	35%	18 (11, 25)	7%	23%	16 (6, 26)
Sustained Virologic Response	11%	26%	15 (8, 23)	19%	38%	19 (11, 26)	8%	30%	22 (11, 33)

144 *Percent difference between PEGASYS and ROFERON-A treatment.

145

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

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149 Of the patients who did not demonstrate either undetectable HCV RNA or at least a
150 $2\log_{10}$ drop in HCV RNA titer from baseline by 12 weeks of PEGASYS 180 µg therapy,
151 2% (3/156) achieved a sustained virologic response (see **DOSAGE AND**
152 **ADMINISTRATION**).

153 Averaged over Study 1, Study 2, and Study 3, response rates to PEGASYS were 23%
154 among patients with viral genotype 1 and 48% in patients with other viral genotypes. The
155 treatment response rates were similar in men and women.

156 **Chronic Hepatitis C Studies 4 and 5: PEGASYS/COPEGUS Combination** 157 **Therapy**

158 The safety and effectiveness of PEGASYS in combination with COPEGUS for the
159 treatment of hepatitis C virus infection were assessed in two randomized controlled
160 clinical trials. All patients were adults, had compensated liver disease, detectable hepatitis
161 C virus, liver biopsy diagnosis of chronic hepatitis, and were previously untreated with
162 interferon. Approximately 20% of patients in both studies had compensated cirrhosis
163 (Child-Pugh class A). Patients coinfecting with HIV were excluded from these studies.

164 In Study 4, patients were randomized to receive either PEGASYS 180 µg sc once weekly
165 (qw) with an oral placebo, PEGASYS 180 µg qw with COPEGUS 1000 mg po (body
166 weight <75 kg) or 1200 mg po (body weight ≥75 kg) or REBETRON (interferon alfa-2b
167 3 MIU sc tiw plus ribavirin 1000 mg or 1200 mg po). All patients received 48 weeks of
168 therapy followed by 24 weeks of treatment-free follow-up. COPEGUS or placebo
169 treatment assignment was blinded. Sustained virological response was defined as
170 undetectable (<50 IU/mL) HCV RNA on or after study week 68. PEGASYS in
171 combination with COPEGUS resulted in a higher SVR compared to PEGASYS alone or
172 interferon alfa-2b and ribavirin (Table 2). In all treatment arms, patients with viral
173 genotype 1, regardless of viral load, had a lower response rate.

174 **Table 2 Sustained Virologic Response to Combination Therapy**
175 **(Study 4)**

	Interferon alfa-2b + Ribavirin 1000 mg or 1200 mg	PEGASYS + Placebo	PEGASYS + COPEGUS 1000 mg or 1200 mg
All patients	197/444 (44%)*	65/224 (29%)	241/453 (53%)*
Genotype 1	103/285 (36%)	29/145 (20%)	132/298 (44%)
Genotypes 2-6	94/159 (59%)	36/79 (46%)	109/155 (70%)

176 *Difference in overall treatment response (PEGASYS/COPEGUS – Interferon alfa-2b/ribavirin) was 9%
177 (95% CI 2.3, 15.3).
178

179 In Study 5 (see Table 3), all patients received PEGASYS 180 µg sc qw and were
180 randomized to treatment for either 24 or 48 weeks and to a COPEGUS dose of either
181 800 mg or 1000 mg/1200 mg (for body weight <75 kg / ≥75 kg). Assignment to the four
182 treatment arms was stratified by viral genotype and baseline HCV viral titer. Patients

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183 with genotype 1 and high viral titer (defined as $>2 \times 10^6$ HCV RNA copies/mL serum)
184 were preferentially assigned to treatment for 48 weeks.

185 HCV Genotypes

186 HCV 1 and 4 – Irrespective of baseline viral titer, treatment for 48 weeks with
187 PEGASYS and 1000 mg or 1200 mg of COPEGUS resulted in higher SVR (defined as
188 undetectable HCV RNA at the end of the 24-week treatment-free follow-up period)
189 compared to shorter treatment (24 weeks) and/or 800 mg COPEGUS.

190 HCV 2 and 3 – Irrespective of baseline viral titer, treatment for 24 weeks with
191 PEGASYS and 800 mg of COPEGUS resulted in a similar SVR compared to longer
192 treatment (48 weeks) and/or 1000 mg or 1200 mg of COPEGUS (see Table 3).

193 The numbers of patients with genotype 5 and 6 were too few to allow for meaningful
194 assessment.

195 **Table 3 Sustained Virologic Response as a Function of Genotype**
196 **(Study 5)**

	24 Weeks Treatment		48 Weeks Treatment	
	PEGASYS + COPEGUS 800 mg (N=207)	PEGASYS + COPEGUS 1000 mg or 1200 mg* (N=280)	PEGASYS + COPEGUS 800 mg (N=361)	PEGASYS + COPEGUS 1000 mg or 1200 mg* (N=436)
Genotype 1	29/101 (29%)	48/118 (41%)	99/250 (40%)	138/271 (51%)
Genotypes 2, 3	79/96 (82%)	116/144 (81%)	75/99 (76%)	117/153 (76%)
Genotype 4	0/5 (0%)	7/12 (58%)	5/8 (63%)	9/11 (82%)

197 *1000 mg for body weight <75 kg; 1200 mg for body weight \geq 75 kg.

198 Other Treatment Response Predictors

199 Treatment response rates are lower in patients with poor prognostic factors receiving
200 pegylated interferon alpha therapy. In studies 4 and 5, treatment response rates were
201 lower in patients older than 40 years (50% vs. 66%), in patients with cirrhosis (47% vs.
202 59%), in patients weighing over 85 kg (49% vs. 60%), and in patients with genotype 1
203 with high vs. low viral load (43% vs. 56%). African-American patients had lower
204 response rates compared to Caucasians.

205 Paired liver biopsies were performed on approximately 20% of patients in studies 4 and
206 5. Modest reductions in inflammation compared to baseline were seen in all treatment
207 groups.

208 In studies 4 and 5, lack of early virologic response by 12 weeks (defined as HCV RNA
209 undetectable or $>2\log_{10}$ lower than baseline) was grounds for discontinuation of
210 treatment. Of patients who lacked an early viral response by 12 weeks and completed a

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211 recommended course of therapy despite a protocol-defined option to discontinue therapy,
212 5/39 (13%) achieved an SVR. Of patients who lacked an early viral response by 24
213 weeks, 19 completed a full course of therapy and none achieved an SVR.

214 **Chronic Hepatitis C and Coinfection with HIV (CHC/HIV) Study 6:** 215 **PEGASYS Monotherapy and PEGASYS/COPEGUS Combination** 216 **Therapy**

217 In Study 6, patients with CHC/HIV were randomized to receive either PEGASYS 180 µg
218 sc once weekly (qw) plus an oral placebo, PEGASYS 180 µg qw plus COPEGUS
219 800 mg po daily or ROFERON-A (interferon alfa-2a), 3 MIU sc tiw plus COPEGUS 800
220 mg po daily. All patients received 48 weeks of therapy and sustained virologic response
221 (SVR) was assessed at 24 weeks of treatment-free follow-up. COPEGUS or placebo
222 treatment assignment was blinded in the PEGASYS treatment arms. All patients were
223 adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis
224 of chronic hepatitis C, and were previously untreated with interferon. Patients also had
225 CD4+ cell count ≥ 200 cells/ μL or CD4+ cell count ≥ 100 cells/ μL but < 200 cells/ μL and
226 HIV-1 RNA < 5000 copies/mL, and stable status of HIV. Approximately 15% of patients
227 in the study had cirrhosis. Results are shown in Table 4.

228 **Table 4 Sustained Virologic Response in Patients with Chronic**
229 **Hepatitis C Coinfected with HIV (Study 6)**

	ROFERON-A + COPEGUS 800 mg (N=289)	PEGASYS + Placebo (N=289)	PEGASYS + COPEGUS 800 mg (N=290)
All patients	33 (11%)*	58 (20%)*	116 (40%)
Genotype 1	12/171 (7%)	24/175 (14%)	51/176 (29%)
Genotypes 2, 3	18/89 (20%)	32/90 (36%)	59/95 (62%)

230 *PEGASYS + COPEGUS vs. PEGASYS; PEGASYS + COPEGUS vs. ROFERON-A + COPEGUS p-
231 value < 0.0001 (Cochran-Mantel-Haenszel).
232

233 Treatment response rates are lower in CHC/HIV patients with poor prognostic factors
234 (including HCV genotype 1, HCV RNA $> 800,000$ IU/mL, and cirrhosis) receiving
235 pegylated interferon alpha therapy. Geographic region is not a prognostic factor for
236 response. However, poor prognostic factors occur more frequently in the US population
237 than in the non-US population.

238 Of the patients who did not demonstrate either undetectable HCV RNA or at least a
239 $2\log_{10}$ reduction from baseline in HCV RNA titer by 12 weeks of PEGASYS and
240 COPEGUS combination therapy, 2% (2/85) achieved an SVR.

241 In CHC patients with HIV coinfection who received 48 weeks of PEGASYS alone or in
242 combination with COPEGUS treatment, mean and median HIV RNA titers did not
243 increase above baseline during treatment or 24 weeks post-treatment.

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244 **Chronic Hepatitis B Studies 7 and 8: PEGASYS Monotherapy**

245 The safety and effectiveness of PEGASYS for the treatment of chronic hepatitis B were
246 assessed in controlled clinical trials in HBeAg positive (Study 7) and HBeAg negative
247 (Study 8) patients with chronic hepatitis B.

248 Patients were randomized to PEGASYS 180 µg sc once weekly (qw), PEGASYS 180 µg
249 sc qw combined with lamivudine 100 mg once daily po or lamivudine 100 mg once daily
250 po. All patients received 48 weeks of their assigned therapy followed by 24 weeks of
251 treatment-free follow-up. Assignment to receipt of PEGASYS or no PEGASYS was not
252 masked.

253 All patients were adults with compensated liver disease, had chronic hepatitis B virus
254 (HBV) infection, and evidence of HBV replication (serum HBV >500,000 copies/mL for
255 Study 7 and >100,000 copies/mL for Study 8) as measured by PCR (COBAS
256 AMPLICOR HBV Assay). All patients had serum alanine aminotransferase (ALT)
257 between 1 and 10 times the upper limit of normal (ULN) and liver biopsy findings
258 compatible with the diagnosis of chronic hepatitis.

259 The results observed in the PEGASYS and lamivudine monotherapy groups are shown in
260 Table 5.

261 **Table 5 Percentage of Patients with Serological, Virological,**
262 **Biochemical, and Histological Response**

	Study 7 HBeAg positive			Study 8 HBeAg negative		
	Lamivudine N = 272	PEGASYS N = 271	PEGASYS N = 271	Lamivudine N = 181	PEGASYS N = 177	PEGASYS N = 177
	EOT ¹	EOF ²	EOF ²	EOT ¹	EOF ²	EOF ²
HBeAg Seroconversion (%)	20	19*	32*	NA	NA	NA
HBV DNA Response (%) ³	62	22***	32***	85	29**	43**
ALT Normalization (%)	62	28	41	73	44**	59**
HBsAg Seroconversion (%)	0	0	3	1	0	3
	N = 184		N = 207	N = 125		N = 143
Histological Improvement (%) ⁴	ND	40	41	ND	41	48
Changes in Ishak fibrosis score compared to baseline (%): - Improved ⁵	ND	32	25	ND	31	32

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- Unchanged		20	25		23	30
- Worsened ⁵		16	26		15	19

263 ¹End of Treatment (week 48)

264 ²End of follow-up – 24 weeks post-treatment (week 72)

265 ³<100,000 copies/mL for HBeAg positive and <20,000 copies/mL for HBeAg negative patients

266 ⁴≥2 point decrease in Ishak necro-inflammatory score from baseline with no worsening of the Ishak fibrosis

267 score. Not all patients provided both initial and end of follow-up biopsies (missing biopsy rates: 19% to

268 24% in the PEGASYS and 31% to 32% in the Lamivudine arms)

269 ⁵Change of 1 point or more in Ishak fibrosis score

270 *p<0.001; **p<0.01; ***p=0.012 (primary efficacy endpoints Cochran-Mantel-Haenszel test comparisons
271 of PEGASYS to Lamivudine)

272

273 PEGASYS co-administered with lamivudine did not result in any additional sustained
274 response when compared to PEGASYS monotherapy.

275 Conclusions regarding comparative efficacy of PEGASYS and lamivudine treatment
276 based upon the end of follow-up results are limited by the different mechanisms of action
277 of the two compounds. Most treatment effects of lamivudine are unlikely to persist 24
278 weeks after therapy is withdrawn.

279 INDICATIONS AND USAGE

280 PEGASYS, peginterferon alfa-2a, alone or in combination with COPEGUS, is indicated
281 for the treatment of adults with chronic hepatitis C virus infection who have compensated
282 liver disease and have not been previously treated with interferon alpha. Patients in whom
283 efficacy was demonstrated included patients with compensated liver disease and
284 histological evidence of cirrhosis (Child-Pugh class A) and patients with HIV disease that
285 is clinically stable (e.g., antiretroviral therapy not required or receiving stable
286 antiretroviral therapy).

287 PEGASYS is indicated for the treatment of adult patients with HBeAg positive and
288 HBeAg negative chronic hepatitis B who have compensated liver disease and evidence of
289 viral replication and liver inflammation.

290 CONTRAINDICATIONS

291 PEGASYS is contraindicated in patients with:

- 292 • Hypersensitivity to PEGASYS or any of its components
- 293 • Autoimmune hepatitis
- 294 • Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in
295 cirrhotic patients before or during treatment
- 296 • Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic
297 CHC patients coinfecting with HIV before or during treatment

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298 PEGASYS is contraindicated in neonates and infants because it contains benzyl alcohol.
299 Benzyl alcohol is associated with an increased incidence of neurologic and other
300 complications in neonates and infants, which are sometimes fatal.

301 PEGASYS and COPEGUS combination therapy is additionally contraindicated in:

- 302 • Patients with known hypersensitivity to COPEGUS or to any component of the tablet
- 303 • Women who are pregnant
- 304 • Men whose female partners are pregnant
- 305 • Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)

WARNINGS

General

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

Neuropsychiatric

312 Life-threatening or fatal neuropsychiatric reactions may manifest in patients receiving
313 therapy with PEGASYS and include suicide, suicidal ideation, homicidal ideation,
314 depression, relapse of drug addiction, and drug overdose. These reactions may occur in
315 patients with and without previous psychiatric illness.

316 PEGASYS should be used with extreme caution in patients who report a history of
317 depression. Neuropsychiatric adverse events observed with alpha interferon treatment
318 include aggressive behavior, psychoses, hallucinations, bipolar disorders, and mania.
319 Physicians should monitor all patients for evidence of depression and other psychiatric
320 symptoms. Patients should be advised to report any sign or symptom of depression or
321 suicidal ideation to their prescribing physicians. In severe cases, therapy should be
322 stopped immediately and psychiatric intervention instituted (see **ADVERSE**
323 **REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Infections

325 Serious and severe bacterial infections, some fatal, have been observed in patients treated
326 with alpha interferons including PEGASYS. Some of the infections have been associated
327 with neutropenia. PEGASYS should be discontinued in patients who develop severe
328 infections and appropriate antibiotic therapy instituted.

Bone Marrow Toxicity

330 PEGASYS suppresses bone marrow function and may result in severe cytopenias.
331 Ribavirin may potentiate the neutropenia and lymphopenia induced by alpha interferons
332 including PEGASYS. Very rarely alpha interferons may be associated with aplastic
333 anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and
334 monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**).

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335 PEGASYS and COPEGUS should be used with caution in patients with baseline
336 neutrophil counts <1500 cells/mm³, with baseline platelet counts $<90,000$ cells/mm³ or
337 baseline hemoglobin <10 g/dL. PEGASYS therapy should be discontinued, at least
338 temporarily, in patients who develop severe decreases in neutrophil and/or platelet counts
339 (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

340 Severe neutropenia and thrombocytopenia occur with a greater incidence in HIV
341 coinfecting patients than mono-infected patients and may result in serious infections or
342 bleeding (see **ADVERSE REACTIONS**).

343 **Cardiovascular Disorders**

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

346 PEGASYS should be administered with caution to patients with pre-existing cardiac
347 disease. Because cardiac disease may be worsened by ribavirin-induced anemia, patients
348 with a history of significant or unstable cardiac disease should not use COPEGUS (see
349 **WARNINGS: Anemia and COPEGUS Package Insert**).

350 **Hepatic Failure and Hepatitis Exacerbations**

351 Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic
352 decompensation and death when treated with alpha interferons, including PEGASYS.
353 Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy
354 (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk
355 for the development of hepatic decompensation compared to patients not receiving
356 HAART. In Study 6, among 129 CHC/HIV cirrhotic patients receiving HAART, 14
357 (11%) of these patients across all treatment arms developed hepatic decompensation
358 resulting in 6 deaths. All 14 patients were on NRTIs, including stavudine, didanosine,
359 abacavir, zidovudine, and lamivudine. These small numbers of patients do not permit
360 discrimination between specific NRTIs for the associated risk. During treatment,
361 patients' clinical status and hepatic function should be closely monitored, and PEGASYS
362 treatment should be immediately discontinued if decompensation (Child-Pugh score ≥ 6)
363 is observed (see **CONTRAINDICATIONS**).

364 Exacerbations of hepatitis during hepatitis B therapy are not uncommon and are
365 characterized by transient and potentially severe increases in serum ALT. Chronic
366 hepatitis B patients experienced transient acute exacerbations (flares) of hepatitis B (ALT
367 elevation >10 -fold higher than the upper limit of normal) during PEGASYS treatment
368 (12% and 18%) and post-treatment (7% and 12%) in HBeAg negative and HBeAg
369 positive patients, respectively. Marked transaminase flares while on PEGASYS therapy
370 have been accompanied by other liver test abnormalities. Patients experiencing ALT
371 flares should receive more frequent monitoring of liver function. PEGASYS dose
372 reduction should be considered in patients experiencing transaminase flares. If ALT
373 increases are progressive despite reduction of PEGASYS dose or are accompanied by
374 increased bilirubin or evidence of hepatic decompensation, PEGASYS should be
375 immediately discontinued (see **ADVERSE REACTIONS: Chronic Hepatitis B** and
376 **DOSAGE AND ADMINISTRATION: Dose Modifications**).

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377 Hypersensitivity

378 Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction,
379 and anaphylaxis) have been rarely observed during alpha interferon and ribavirin therapy.
380 If such reaction occurs, therapy with PEGASYS and COPEGUS should be discontinued
381 and appropriate medical therapy immediately instituted.

382 Endocrine Disorders

383 PEGASYS causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia,
384 hypoglycemia, and diabetes mellitus have been observed to develop in patients treated
385 with PEGASYS. Patients with these conditions at baseline who cannot be effectively
386 treated by medication should not begin PEGASYS therapy. Patients who develop these
387 conditions during treatment and cannot be controlled with medication may require
388 discontinuation of PEGASYS therapy.

389 Autoimmune Disorders

390 Development or exacerbation of autoimmune disorders including myositis, hepatitis,
391 thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, psoriasis,
392 rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus
393 have been reported in patients receiving alpha interferon. PEGASYS should be used with
394 caution in patients with autoimmune disorders.

395 Pulmonary Disorders

396 Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial
397 pneumonitis and sarcoidosis, some resulting in respiratory failure and/or patient deaths,
398 may be induced or aggravated by PEGASYS or alpha interferon therapy. Patients who
399 develop persistent or unexplained pulmonary infiltrates or pulmonary function
400 impairment should discontinue treatment with PEGASYS.

401 Colitis

402 Ulcerative and hemorrhagic/ischemic colitis, sometimes fatal, have been observed within
403 12 weeks of starting alpha interferon treatment. Abdominal pain, bloody diarrhea, and
404 fever are the typical manifestations of colitis. PEGASYS should be discontinued
405 immediately if these symptoms develop. The colitis usually resolves within 1 to 3 weeks
406 of discontinuation of alpha interferon.

407 Pancreatitis

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

412 Ophthalmologic Disorders

413 Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein
414 thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema
415 are induced or aggravated by treatment with PEGASYS or other alpha interferons. All
416 patients should receive an eye examination at baseline. Patients with pre-existing
417 ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive

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418 periodic ophthalmologic exams during interferon alpha treatment. Any patient who
419 develops ocular symptoms should receive a prompt and complete eye examination.
420 PEGASYS treatment should be discontinued in patients who develop new or worsening
421 ophthalmologic disorders.

422 **Pregnancy: Use with Ribavirin (also, see COPEGUS Package Insert)**

423 **Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care**
424 **must be taken to avoid pregnancy in female patients and in female partners of male**
425 **patients taking PEGASYS and COPEGUS combination therapy. COPEGUS**
426 **THERAPY SHOULD NOT BE STARTED UNLESS A REPORT OF A**
427 **NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY**
428 **PRIOR TO INITIATION OF THERAPY. Women of childbearing potential and**
429 **men must use two forms of effective contraception during treatment and for at least**
430 **6 months after treatment has concluded. Routine monthly pregnancy tests must be**
431 **performed during this time (see BOXED WARNING, CONTRAINDICATIONS,**
432 **PRECAUTIONS: Information for Patients, and COPEGUS Package Insert).**

433 **Anemia**

434 The primary toxicity of ribavirin is hemolytic anemia. Hemoglobin <10 g/dL was
435 observed in approximately 13% of COPEGUS and PEGASYS treated patients in chronic
436 hepatitis C clinical trials (see **PRECAUTIONS: Laboratory Tests**). The anemia
437 associated with COPEGUS occurs within 1 to 2 weeks of initiation of therapy with
438 maximum drop in hemoglobin observed during the first eight weeks. BECAUSE THE
439 INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT
440 HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRE-TREATMENT AND AT
441 WEEK 2 AND WEEK 4 OF THERAPY OR MORE FREQUENTLY IF CLINICALLY
442 INDICATED. Patients should then be followed as clinically appropriate.

443 Fatal and nonfatal myocardial infarctions have been reported in patients with anemia
444 caused by ribavirin. Patients should be assessed for underlying cardiac disease before
445 initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have
446 electrocardiograms administered before treatment, and should be appropriately monitored
447 during therapy. If there is any deterioration of cardiovascular status, therapy should be
448 suspended or discontinued (see **DOSAGE AND ADMINISTRATION: COPEGUS**
449 **Dosage Modification Guidelines**). Because cardiac disease may be worsened by drug-
450 induced anemia, patients with a history of significant or unstable cardiac disease should
451 not use COPEGUS (see **COPEGUS Package Insert**).

452 **Renal**

453 It is recommended that renal function be evaluated in all patients started on COPEGUS.
454 COPEGUS should not be administered to patients with creatinine clearance <50 mL/min
455 (see **CLINICAL PHARMACOLOGY: Special Populations**).

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456 PRECAUTIONS

457 General

458 The safety and efficacy of PEGASYS alone or in combination with COPEGUS have not
459 been established in:

- 460 • Patients who have failed alpha interferon treatment with or without ribavirin
- 461 • Liver or other organ transplant recipients
- 462 • Hepatitis B patients coinfecting with HCV or HIV
- 463 • Hepatitis C patients coinfecting with HBV or coinfecting with HIV with a CD4+ cell
464 count <100 cells/μL
465

466 Caution should be exercised in initiating treatment in any patient with baseline risk of
467 severe anemia (e.g., spherocytosis, history of GI bleeding).

468 Renal Impairment

469 A 25% to 45% higher exposure to PEGASYS is seen in subjects undergoing
470 hemodialysis. In patients with impaired renal function, signs and symptoms of interferon
471 toxicity should be closely monitored. Doses of PEGASYS should be adjusted
472 accordingly. PEGASYS should be used with caution in patients with creatinine clearance
473 <50 mL/min (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

474 COPEGUS should not be used in patients with creatinine clearance <50 mL/min (see
475 **COPEGUS Package Insert**).

476 Information for Patients

477 Patients receiving PEGASYS alone or in combination with COPEGUS should be
478 directed in its appropriate use, informed of the benefits and risks associated with
479 treatment, and referred to the PEGASYS and, if applicable, COPEGUS (ribavirin)
480 MEDICATION GUIDES.

481 PEGASYS and COPEGUS combination therapy must not be used by women who are
482 pregnant or by men whose female partners are pregnant. COPEGUS therapy should not
483 be initiated until a report of a negative pregnancy test has been obtained immediately
484 before starting therapy. Female patients of childbearing potential and male patients with
485 female partners of childbearing potential must be advised of the teratogenic/embryocidal
486 risks and must be instructed to practice effective contraception during COPEGUS therapy
487 and for 6 months post-therapy. Patients should be advised to notify the healthcare
488 provider immediately in the event of a pregnancy (see **CONTRAINDICATIONS** and
489 **WARNINGS**).

490 Women of childbearing potential and men must use two forms of effective contraception
491 during treatment and during the 6 months after treatment has been stopped; routine
492 monthly pregnancy tests must be performed during this time (see
493 **CONTRAINDICATIONS** and **COPEGUS Package Insert**).

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494 To monitor maternal and fetal outcomes of pregnant women exposed to COPEGUS, the
495 Ribavirin Pregnancy Registry has been established. Patients should be encouraged to
496 register by calling 1-800-593-2214.

497 Patients should be advised that laboratory evaluations are required before starting therapy
498 and periodically thereafter (see **Laboratory Tests**). Patients should be instructed to
499 remain well hydrated, especially during the initial stages of treatment. Patients should be
500 advised to take COPEGUS with food.

501 Patients should be informed that it is not known if therapy with PEGASYS alone or in
502 combination with COPEGUS will prevent transmission of HCV or HBV infection to
503 others or prevent cirrhosis, liver failure or liver cancer that might result from HCV or
504 HBV infection. Patients who develop dizziness, confusion, somnolence, and fatigue
505 should be cautioned to avoid driving or operating machinery.

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

511 **Laboratory Tests**

512 Before beginning PEGASYS or PEGASYS and COPEGUS combination therapy,
513 standard hematological and biochemical laboratory tests are recommended for all
514 patients. Pregnancy screening for women of childbearing potential must be performed.

515 After initiation of therapy, hematological tests should be performed at 2 weeks and 4
516 weeks and biochemical tests should be performed at 4 weeks. Additional testing should
517 be performed periodically during therapy. In the clinical studies, the CBC (including
518 hemoglobin level and white blood cell and platelet counts) and chemistries (including
519 liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8 weeks, and then
520 every 4 to 6 weeks or more frequently if abnormalities were found. Thyroid stimulating
521 hormone (TSH) was measured every 12 weeks. Monthly pregnancy testing should be
522 performed during combination therapy and for 6 months after discontinuing therapy.

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

- 525 • Platelet count $\geq 90,000$ cells/mm³ (as low as 75,000 cells/mm³ in HCV patients with
526 cirrhosis or 70,000 cells/mm³ in patients with CHC and HIV)
- 527 • Absolute neutrophil count (ANC) ≥ 1500 cells/mm³
- 528 • Serum creatinine concentration < 1.5 x upper limit of normal
- 529 • TSH and T₄ within normal limits or adequately controlled thyroid function
- 530 • CD4⁺ cell count ≥ 200 cells/ μ L or CD4⁺ cell count ≥ 100 cells/ μ L but < 200 cells/ μ L
531 and HIV-1 RNA < 5000 copies/mL in patients coinfecting with HIV

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532 • Hemoglobin ≥ 12 g/dL for women and ≥ 13 g/dL for men in CHC monoinfected
533 patients

534 • Hemoglobin ≥ 11 g/dL for women and ≥ 12 g/dL for men in patients with CHC and
535 HIV

536 PEGASYS treatment was associated with decreases in WBC, ANC, lymphocytes, and
537 platelet counts often starting within the first 2 weeks of treatment (see **ADVERSE**
538 **REACTIONS**). Dose reduction is recommended in patients with hematologic
539 abnormalities (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

540 While fever is commonly caused by PEGASYS therapy, other causes of persistent fever
541 must be ruled out, particularly in patients with neutropenia (see **WARNINGS:**
542 **Infections**).

543 In chronic hepatitis C, transient elevations in ALT (2-fold to 5-fold above baseline) were
544 observed in some patients receiving PEGASYS, and were not associated with
545 deterioration of other liver function tests. When the increase in ALT levels is progressive
546 despite dose reduction or is accompanied by increased bilirubin, PEGASYS therapy
547 should be discontinued (see **DOSAGE AND ADMINISTRATION: Dose**
548 **Modifications**).

549 Unlike hepatitis C, during hepatitis B therapy and follow up, transient elevations in ALT
550 of 5 to 10 x ULN were observed in 25% and 27% and of >10 x ULN were observed in
551 12% and 18%, of HBeAg negative and HBeAg positive patients, respectively. These
552 ALT elevations have been accompanied by other liver test abnormalities (see
553 **WARNINGS: Hepatic Failure and Hepatitis Exacerbations** and **DOSAGE AND**
554 **ADMINISTRATION: Dose Modifications**).

555 **Drug Interactions**

556 Theophylline

557 Treatment with PEGASYS once weekly for 4 weeks in healthy subjects was associated
558 with an inhibition of P450 1A2 and a 25% increase in theophylline AUC. Theophylline
559 serum levels should be monitored and appropriate dose adjustments considered for
560 patients given both theophylline and PEGASYS (see **CLINICAL PHARMACOLOGY:**
561 **Drug Interactions**).

562 Methadone

563 In a PK study of HCV patients concomitantly receiving methadone, treatment with
564 PEGASYS once weekly for 4 weeks was associated with methadone levels that were
565 10% to 15% higher than at baseline (see **CLINICAL PHARMACOLOGY: Drug**
566 **Interactions**). The clinical significance of this finding is unknown; however, patients
567 should be monitored for the signs and symptoms of methadone toxicity.

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568 Nucleoside Analogues

569 *NRTIs*

570 In Study 6 among the CHC/HIV coinfecting cirrhotic patients receiving NRTIs cases of
571 hepatic decompensation (some fatal) were observed (see **WARNINGS: Hepatic Failure**
572 **and Hepatitis Exacerbations**).

573 Patients receiving PEGASYS/COPEGUS and NRTIs should be closely monitored for
574 treatment associated toxicities. Physicians should refer to prescribing information for the
575 respective NRTIs for guidance regarding toxicity management. In addition, dose
576 reduction or discontinuation of PEGASYS, COPEGUS or both should also be considered
577 if worsening toxicities are observed (see **WARNINGS, PRECAUTIONS, DOSAGE**
578 **AND ADMINISTRATION: Dose Modifications**).

579 *Didanosine*

580 Co-administration of COPEGUS and didanosine is not recommended. Reports of fatal
581 hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic
582 hyperlactatemia/lactic acidosis have been reported in clinical trials (see **CLINICAL**
583 **PHARMACOLOGY: Drug Interactions**).

584 *Zidovudine*

585 In Study 6, patients who were administered zidovudine in combination with
586 PEGASYS/COPEGUS developed severe neutropenia (ANC <500) and severe anemia
587 (hemoglobin <8 g/dL) more frequently than similar patients not receiving zidovudine
588 (neutropenia 15% vs. 9%) (anemia 5% vs. 1%).

589 *Lamivudine, Stavudine, and Zidovudine*

590 In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine
591 nucleoside analogs such as lamivudine, stavudine, and zidovudine. No evidence of a
592 pharmacokinetic or pharmacodynamic interaction was seen when ribavirin was co-
593 administered with lamivudine, stavudine, and/or zidovudine in HIV/HCV coinfecting
594 patients (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

595 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

596 **Carcinogenesis**

597 PEGASYS has not been tested for its carcinogenic potential.

598 **Mutagenesis**

599 PEGASYS did not cause DNA damage when tested in the Ames bacterial mutagenicity
600 assay and in the in vitro chromosomal aberration assay in human lymphocytes, either in
601 the presence or absence of metabolic activation.

602 *Use with Ribavirin*

603 Ribavirin is genotoxic and mutagenic. The carcinogenic potential of ribavirin has not
604 been fully determined. In a p53 (+/-) mouse carcinogenicity study at doses up to the
605 maximum tolerated dose of 100 mg/kg/day ribavirin was not oncogenic. However, on a
606 body surface area basis, this dose was 0.5 times maximum recommended human 24-hour

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607 dose of ribavirin. A study in rats to assess the carcinogenic potential of ribavirin is
608 ongoing (see **COPEGUS Package Insert**).

609 Impairment of Fertility

610 PEGASYS may impair fertility in women. Prolonged menstrual cycles and/or
611 amenorrhea were observed in female cynomolgus monkeys given sc injections of
612 600 µg/kg/dose (7200 µg/m²/dose) of PEGASYS every other day for one month, at
613 approximately 180 times the recommended weekly human dose for a 60 kg person (based
614 on body surface area). Menstrual cycle irregularities were accompanied by both a
615 decrease and delay in the peak 17β-estradiol and progesterone levels following
616 administration of PEGASYS to female monkeys. A return to normal menstrual rhythm
617 followed cessation of treatment. Every other day dosing with 100 µg/kg (1200 µg/m²)
618 PEGASYS (equivalent to approximately 30 times the recommended human dose) had no
619 effects on cycle duration or reproductive hormone status.

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

623 *Use with Ribavirin*

624 Ribavirin has shown reversible toxicity in animal studies of male fertility (see
625 **COPEGUS Package Insert**).

626 **Pregnancy**

627 **Pregnancy: Category C**

628 PEGASYS has not been studied for its teratogenic effect. Non-pegylated interferon alfa-
629 2a treatment of pregnant Rhesus monkeys at approximately 20 to 500 times the human
630 weekly dose resulted in a statistically significant increase in abortions. No teratogenic
631 effects were seen in the offspring delivered at term. PEGASYS should be assumed to
632 have abortifacient potential. There are no adequate and well-controlled studies of
633 PEGASYS in pregnant women. PEGASYS is to be used during pregnancy only if the
634 potential benefit justifies the potential risk to the fetus. PEGASYS is recommended for
635 use in women of childbearing potential only when they are using effective contraception
636 during therapy.

637 **Pregnancy: Category X: Use With Ribavirin (see CONTRAINDICATIONS)**

638 **Significant teratogenic and/or embryocidal effects have been demonstrated in all**
639 **animal species exposed to ribavirin. COPEGUS therapy is contraindicated in**
640 **women who are pregnant and in the male partners of women who are pregnant (see**
641 **CONTRAINDICATIONS, WARNINGS, and COPEGUS Package Insert).**

642 *Ribavirin Pregnancy Registry*

643 A Ribavirin Pregnancy Registry has been established to monitor maternal and fetal
644 outcomes of pregnancies of female patients and female partners of male patients exposed
645 to ribavirin during treatment and for 6 months following cessation of treatment.
646 Healthcare providers and patients are encouraged to report such cases by calling 1-800-
647 593-2214.

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648 **Nursing Mothers**

649 It is not known whether peginterferon or ribavirin or its components are excreted in
650 human milk. The effect of orally ingested peginterferon or ribavirin from breast milk on
651 the nursing infant has not been evaluated. Because of the potential for adverse reactions
652 from the drugs in nursing infants, a decision must be made whether to discontinue
653 nursing or discontinue PEGASYS and COPEGUS treatment.

654 **Pediatric Use**

655 The safety and effectiveness of PEGASYS, alone or in combination with COPEGUS in
656 patients below the age of 18 years have not been established.

657 PEGASYS contains benzyl alcohol. Benzyl alcohol has been reported to be associated
658 with an increased incidence of neurological and other complications in neonates and
659 infants, which are sometimes fatal (see **CONTRAINDICATIONS**).

660 **Geriatric Use**

661 Younger patients have higher virologic response rates than older patients. Clinical studies
662 of PEGASYS alone or in combination with COPEGUS did not include sufficient
663 numbers of subjects aged 65 or over to determine whether they respond differently from
664 younger subjects. Adverse reactions related to alpha interferons, such as CNS, cardiac,
665 and systemic (e.g., flu-like) effects may be more severe in the elderly and caution should
666 be exercised in the use of PEGASYS in this population. PEGASYS and COPEGUS are
667 excreted by the kidney, and the risk of toxic reactions to this therapy may be greater in
668 patients with impaired renal function. Because elderly patients are more likely to have
669 decreased renal function, care should be taken in dose selection and it may be useful to
670 monitor renal function. PEGASYS should be used with caution in patients with creatinine
671 clearance <50 mL/min and COPEGUS should not be administered to patients with
672 creatinine clearance <50 mL/min.

673 **ADVERSE REACTIONS**

674 PEGASYS alone or in combination with COPEGUS causes a broad variety of serious
675 adverse reactions (see **BOXED WARNING** and **WARNINGS**). The most common life-
676 threatening or fatal events induced or aggravated by PEGASYS and COPEGUS were
677 depression, suicide, relapse of drug abuse/overdose, and bacterial infections, each
678 occurring at a frequency of <1%. Hepatic decompensation occurred in 2% (10/574) of
679 CHC/HIV patients (see **WARNINGS: Hepatic Failure and Hepatitis Exacerbations**).

680 In all hepatitis C studies, one or more serious adverse reactions occurred in 10% of CHC
681 monoinfected patients and in 19% of CHC/HIV patients receiving PEGASYS alone or in
682 combination with COPEGUS. The most common serious adverse event (3% in CHC and
683 5% in CHC/HIV) was bacterial infection (e.g., sepsis, osteomyelitis, endocarditis,
684 pyelonephritis, pneumonia). Other SAEs occurred at a frequency of <1% and included:
685 suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose,
686 angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus,
687 autoimmune phenomena (e.g., hyperthyroidism, hypothyroidism, sarcoidosis, systemic
688 lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic

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689 ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism,
690 coma, myositis, cerebral hemorrhage, and thrombotic thrombocytopenic purpura.

691 Nearly all patients in clinical trials experienced one or more adverse events. For hepatitis
692 C patients, the most commonly reported adverse reactions were psychiatric reactions,
693 including depression, insomnia, irritability, anxiety, and flu-like symptoms such as
694 fatigue, pyrexia, myalgia, headache, and rigors. Other common reactions were anorexia,
695 nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

696 Overall 11% of CHC monoinfected patients receiving 48 weeks of therapy with
697 PEGASYS either alone or in combination with COPEGUS discontinued therapy; 16% of
698 CHC/HIV coinfecting patients discontinued therapy. The most common reasons for
699 discontinuation of therapy were psychiatric, flu-like syndrome (e.g., lethargy, fatigue,
700 headache), dermatologic, and gastrointestinal disorders and laboratory abnormalities
701 (thrombocytopenia, neutropenia, and anemia).

702 Overall 39% of patients with CHC or CHC/HIV required modification of PEGASYS
703 and/or COPEGUS therapy. The most common reason for dose modification of
704 PEGASYS in CHC and CHC/HIV patients was for laboratory abnormalities, neutropenia
705 (20% and 27%, respectively) and thrombocytopenia (4% and 6%, respectively). The most
706 common reason for dose modification of COPEGUS in CHC and CHC/HIV patients was
707 anemia (22% and 16%, respectively).

708 PEGASYS dose was reduced in 12% of patients receiving 1000 mg to 1200 mg
709 COPEGUS for 48 weeks and in 7% of patients receiving 800 mg COPEGUS for 24
710 weeks. COPEGUS dose was reduced in 21% of patients receiving 1000 mg to 1200 mg
711 COPEGUS for 48 weeks and in 12% of patients receiving 800 mg COPEGUS for 24
712 weeks.

713 Chronic hepatitis C monoinfected patients treated for 24 weeks with PEGASYS and 800
714 mg COPEGUS were observed to have lower incidence of serious adverse events (3% vs.
715 10%), Hgb <10 g/dL (3% vs. 15%), dose modification of PEGASYS (30% vs. 36%) and
716 COPEGUS (19% vs. 38%) and of withdrawal from treatment (5% vs. 15%) compared to
717 patients treated for 48 weeks with PEGASYS and 1000 mg or 1200 mg COPEGUS. On
718 the other hand the overall incidence of adverse events appeared to be similar in the two
719 treatment groups.

720 **Because clinical trials are conducted under widely varying and controlled**
721 **conditions, adverse reaction rates observed in clinical trials of a drug cannot be**
722 **directly compared to rates in the clinical trials of another drug. Also, the adverse**
723 **event rates listed here may not predict the rates observed in a broader patient**
724 **population in clinical practice.**

725 **Table 6** **Adverse Reactions Occurring in $\geq 5\%$ of Patients in Chronic**
726 **Hepatitis C Clinical Trials (Pooled Studies 1, 2, 3, and**
727 **Study 4)**

	CHC Monotherapy (Pooled Studies 1-3)	CHC Combination Therapy Study 4
--	--------------------------------------	---------------------------------

PEGASYS (peginterferon alfa-2a)

Body System	PEGASYS 180 µg 48 week†	ROFERON-A*†	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week**	Intron A + 1000 mg or 1200 mg REBETOL 48 week**
	N=559	N=554	N=451	N=443
	%	%	%	%
Application Site Disorders				
Injection site reaction	22	18	23	16
Endocrine Disorders				
Hypothyroidism	3	2	4	5
Flu-like Symptoms and Signs				
Fatigue/Asthenia	56	57	65	68
Pyrexia	37	41	41	55
Rigors	35	44	25	37
Pain	11	12	10	9
Gastrointestinal				
Nausea/Vomiting	24	33	25	29
Diarrhea	16	16	11	10
Abdominal pain	15	15	8	9
Dry mouth	6	3	4	7
Dyspepsia	<1	1	6	5
Hematologic‡				
Lymphopenia	3	5	14	12
Anemia	2	1	11	11
Neutropenia	21	8	27	8
Thrombocytopenia	5	2	5	<1
Metabolic and Nutritional				
Anorexia	17	17	24	26
Weight decrease	4	3	10	10
Musculoskeletal, Connective Tissue and Bone				
Myalgia	37	38	40	49
Arthralgia	28	29	22	23
Back pain	9	10	5	5

PEGASYS (peginterferon alfa-2a)

	CHC Monotherapy (Pooled Studies 1-3)		CHC Combination Therapy Study 4	
Body System	PEGASYS 180 µg 48 week†	ROFERON-A*†	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week**	Intron A + 1000 mg or 1200 mg REBETOL 48 week**
	N=559	N=554	N=451	N=443
	%	%	%	%
Neurological				
Headache	54	58	43	49
Dizziness (excluding vertigo)	16	12	14	14
Memory impairment	5	4	6	5
Resistance Mechanism Disorders				
Overall	10	6	12	10
Psychiatric				
Irritability/Anxiety/ Nervousness	19	22	33	38
Insomnia	19	23	30	37
Depression	18	19	20	28
Concentration impairment	8	10	10	13
Mood alteration	3	2	5	6
Respiratory, Thoracic and Mediastinal				
Dyspnea	4	2	13	14
Cough	4	3	10	7
Dyspnea exertional	<1	<1	4	7
Skin and Subcutaneous Tissue				
Alopecia	23	30	28	33
Pruritus	12	8	19	18
Dermatitis	8	3	16	13
Dry skin	4	3	10	13
Rash	5	4	8	5
Sweating increased	6	7	6	5
Eczema	1	1	5	4

PEGASYS (peginterferon alfa-2a)

	CHC Monotherapy (Pooled Studies 1-3)		CHC Combination Therapy Study 4	
Body System	PEGASYS 180 µg 48 week†	ROFERON-A*‡	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week**	Intron A + 1000 mg or 1200 mg REBETOL 48 week**
	N=559	N=554	N=451	N=443
	%	%	%	%
Visual Disorders				
Vision blurred	4	2	5	2

728 † Pooled studies 1, 2, and 3

729 * Either 3 MIU or 6/3 MIU of ROFERON-A

730 **Study 4

731 ‡ Severe hematologic abnormalities (lymphocyte <0.5 x 10⁹/L; hemoglobin <10 g/dL;

732 neutrophil <0.75 x 10⁹/L; platelet <50 x 10⁹/L).

733

734 CHC With HIV Coinfection

735 The adverse event profile of coinfecting patients treated with PEGASYS and COPEGUS
736 in Study 6 was generally similar to that shown for mono-infected patients in Study 4
737 (Table 6). Events occurring more frequently in coinfecting patients were neutropenia
738 (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%), and mood
739 alteration (9%).

740 Chronic Hepatitis B

741 In clinical trials of 48 week treatment duration, the adverse event profile of PEGASYS in
742 chronic hepatitis B was similar to that seen in chronic hepatitis C PEGASYS
743 monotherapy use, except for exacerbations of hepatitis (see **WARNINGS: Hepatic
744 Failure and Hepatitis Exacerbations**). Six percent of PEGASYS treated patients in the
745 hepatitis B studies experienced one or more serious adverse events.

746 The most common or important serious adverse events in the hepatitis B studies were
747 infections (sepsis, appendicitis, tuberculosis, influenza), hepatitis B flares, anaphylactic
748 shock, thrombotic thrombocytopenic purpura.

749 The most commonly observed adverse reactions were pyrexia (54% vs. 4%), headache
750 (27% vs. 9%), fatigue (24% vs. 10%), myalgia (26% vs. 4%), alopecia (18% vs. 2%), and
751 anorexia (16% vs. 3%) in the PEGASYS and lamivudine groups respectively.

752 Overall 5% of hepatitis B patients discontinued PEGASYS therapy and 40% of patients
753 required modification of PEGASYS dose. The most common reason for dose
754 modification in patients receiving PEGASYS therapy was for laboratory abnormalities
755 including neutropenia (20%), thrombocytopenia (13%), and ALT disorders (11%).

PEGASYS (peginterferon alfa-2a)

756 **Laboratory Test Values**

757 The laboratory test values observed in the hepatitis B trials (except where noted below)
758 were similar to those seen in the PEGASYS monotherapy hepatitis C trials.

759 **Neutrophils**

760 In the hepatitis C studies, decreases in neutrophil count below normal were observed in
761 95% of all patients treated with PEGASYS either alone or in combination with
762 COPEGUS. Severe potentially life-threatening neutropenia ($ANC < 0.5 \times 10^9/L$) occurred
763 in 5% of CHC patients and 12% of CHC/HIV patients receiving PEGASYS either alone
764 or in combination with COPEGUS. Modification of PEGASYS dose for neutropenia
765 occurred in 17% of patients receiving PEGASYS monotherapy and 22% of patients
766 receiving PEGASYS/COPEGUS combination therapy. In the CHC/HIV patients 27%
767 required modification of interferon dosage for neutropenia. Two percent of patients with
768 CHC and 10% of patients with CHC/HIV required permanent reductions of PEGASYS
769 dosage and <1% required permanent discontinuation. Median neutrophil counts return to
770 pre-treatment levels 4 weeks after cessation of therapy (see **DOSAGE AND**
771 **ADMINISTRATION: Dose Modifications**).

772 **Lymphocytes**

773 Decreases in lymphocyte count are induced by interferon alpha therapy. PEGASYS plus
774 COPEGUS combination therapy induced decreases in median total lymphocyte counts
775 (56% in CHC and 40% in CHC/HIV, with median decrease of 1170 cells/mm³ in CHC
776 and 800 cells/mm³ in CHC/HIV). In the hepatitis C studies, lymphopenia was observed
777 during both monotherapy (81%) and combination therapy with PEGASYS and
778 COPEGUS (91%). Severe lymphopenia ($< 0.5 \times 10^9/L$) occurred in approximately 5% of
779 all monotherapy patients and 14% of all combination PEGASYS and COPEGUS therapy
780 recipients. Dose adjustments were not required by protocol. The clinical significance of
781 the lymphopenia is not known.

782 In CHC with HIV coinfection, CD4 counts decreased by 29% from baseline (median
783 decrease of 137 cells/mm³) and CD8 counts decreased by 44% from baseline (median
784 decrease of 389 cells/mm³) in the PEGASYS plus COPEGUS combination therapy arm.
785 Median lymphocyte CD4 and CD8 counts return to pre-treatment levels after 4 to 12
786 weeks of the cessation of therapy. CD4% did not decrease during treatment.

787 **Platelets**

788 In the hepatitis C studies, platelet counts decreased in 52% of CHC patients and 51% of
789 CHC/HIV patients treated with PEGASYS alone (respectively median decrease of 41%
790 and 35% from baseline), and in 33% of CHC patients and 47% of CHC/HIV patients
791 receiving combination therapy with COPEGUS (median decrease of 30% from baseline).
792 Moderate to severe thrombocytopenia ($< 50,000/mm^3$) was observed in 4% of CHC and
793 8% of CHC/HIV patients. Median platelet counts return to pre-treatment levels 4 weeks
794 after the cessation of therapy.

PEGASYS (peginterferon alfa-2a)

795 Hemoglobin

796 In the hepatitis C studies, the hemoglobin concentration decreased below 12 g/dL in 17%
797 (median Hgb reduction of 2.2 g/dL) of monotherapy and 52% (median Hgb reduction of
798 3.7 g/dL) of combination therapy patients. Severe anemia (Hgb <10 g/dL) was
799 encountered in 13% of all patients receiving combination therapy and in 2% of CHC
800 patients and 8% of CHC/HIV patients receiving PEGASYS monotherapy. Dose
801 modification for anemia in COPEGUS recipients treated for 48 weeks occurred in 22% of
802 CHC patients and 16% of CHC/HIV patients (see **DOSAGE AND**
803 **ADMINISTRATION: Dose Modifications**).

804 Triglycerides

805 Triglyceride levels are elevated in patients receiving alfa interferon therapy and were
806 elevated in the majority of patients participating in clinical studies receiving either
807 PEGASYS alone or in combination with COPEGUS. Random levels ≥ 400 mg/dL were
808 observed in about 20% of CHC patients. Severe elevations of triglycerides (>1000
809 mg/dL) occurred in 2% of CHC monoinfected patients.

810 In HCV/HIV coinfecting patients, fasting levels ≥ 400 mg/dL were observed in up to 36%
811 of patients receiving either PEGASYS alone or in combination with COPEGUS. Severe
812 elevations of triglycerides (>1000 mg/dL) occurred in 7% of coinfecting patients.

813 ALT Elevations

814 *Chronic Hepatitis C*

815 One percent of patients in the hepatitis C trials experienced marked elevations (5- to 10-
816 fold above the upper limit of normal) in ALT levels during treatment and follow-up.
817 These transaminase elevations were on occasion associated with hyperbilirubinemia and
818 were managed by dose reduction or discontinuation of study treatment. Liver function
819 test abnormalities were generally transient. One case was attributed to autoimmune
820 hepatitis, which persisted beyond study medication discontinuation (see **DOSAGE AND**
821 **ADMINISTRATION: Dose Modifications**).

822 *Chronic Hepatitis B*

823 Transient ALT elevations are common during hepatitis B therapy with PEGASYS.
824 Twenty-five percent and 27% of patients experienced elevations of 5 to 10 x ULN and
825 12% and 18% had elevations of >10 x ULN during treatment of HBeAg negative and
826 HBeAg positive disease, respectively. Flares have been accompanied by elevations of
827 total bilirubin and alkaline phosphatase and less commonly with prolongation of PT and
828 reduced albumin levels. Eleven percent of patients had dose modifications due to ALT
829 flares and $<1\%$ of patients were withdrawn from treatment (see **WARNINGS: Hepatic**
830 **Failure and Hepatitis Exacerbations** and **DOSAGE AND ADMINISTRATION:**
831 **Dose Modifications**).

832 ALT flares of 5 to 10 x ULN occurred in 13% and 16% of patients, while ALT flares of
833 >10 x ULN occurred in 7% and 12% of patients in HBeAg negative and HBeAg positive
834 disease, respectively, after discontinuation of PEGASYS therapy.

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835 Thyroid Function

836 PEGASYS alone or in combination with COPEGUS was associated with the
837 development of abnormalities in thyroid laboratory values, some with associated clinical
838 manifestations. In the hepatitis C studies, hypothyroidism or hyperthyroidism requiring
839 treatment, dose modification or discontinuation occurred in 4% and 1% of PEGASYS
840 treated patients and 4% and 2% of PEGASYS and COPEGUS treated patients,
841 respectively. Approximately half of the patients, who developed thyroid abnormalities
842 during PEGASYS treatment, still had abnormalities during the follow-up period (see
843 **PRECAUTIONS: Laboratory Tests**).

844 Immunogenicity

845 *Chronic Hepatitis C*

846 Nine percent (71/834) of patients treated with PEGASYS with or without COPEGUS
847 developed binding antibodies to interferon alfa-2a, as assessed by an ELISA assay. Three
848 percent of patients (25/835) receiving PEGASYS with or without COPEGUS, developed
849 low-titer neutralizing antibodies (using an assay with a sensitivity of 100 INU/mL).

850 *Chronic Hepatitis B*

851 Twenty-nine percent (42/143) of hepatitis B patients treated with PEGASYS for 24
852 weeks developed binding antibodies to interferon alfa-2a, as assessed by an ELISA assay.
853 Thirteen percent of patients (19/143) receiving PEGASYS developed low-titer
854 neutralizing antibodies (using an assay with a sensitivity of 100 INU/mL).

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

860 Additionally, the observed incidence of antibody positivity in these assays may be
861 influenced by several factors including sample timing and handling, concomitant
862 medications, and underlying disease. For these reasons, comparison of the incidence of
863 antibodies to PEGASYS with the incidence of antibodies to other products may be
864 misleading.

865 Postmarketing Experience

866 The following adverse reactions have been identified and reported during post-approval
867 use of PEGASYS therapy: hearing impairment, hearing loss. Because these reactions are
868 reported voluntarily from a population of uncertain size, it is not always possible to
869 reliably estimate their frequency or establish a causal relationship to drug exposure.
870 Decisions to include these reactions in labeling are typically based on one or more of the
871 following factors: (1) seriousness of the reaction, (2) frequency of reporting or (3)
872 strength of causal connection to PEGASYS.

873 **OVERDOSAGE**

PEGASYS (peginterferon alfa-2a)

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

880 DOSAGE AND ADMINISTRATION

881 There are no safety and efficacy data on treatment of chronic hepatitis C or hepatitis B for
882 longer than 48 weeks. For patients with hepatitis C, consideration should be given to
883 discontinuing therapy after 12 to 24 weeks of therapy if the patient has failed to
884 demonstrate an early virologic response defined as undetectable HCV RNA or at least a
885 2log₁₀ reduction from baseline in HCV RNA titer by 12 weeks of therapy (see
886 **CLINICAL STUDIES**).

887 A patient should self-inject PEGASYS only if the physician determines that it is
888 appropriate and the patient agrees to medical follow-up as necessary and training in
889 proper injection technique has been provided to him/her (see illustrated PEGASYS
890 **MEDICATION GUIDE** for directions on injection site preparation and injection
891 instructions).

892 PEGASYS should be inspected visually for particulate matter and discoloration before
893 administration, and not used if particulate matter is visible or product is discolored. Vials
894 and prefilled syringes with particulate matter or discoloration should be returned to the
895 pharmacist.

896 Chronic Hepatitis C

897 PEGASYS Monotherapy

898 The recommended dose of PEGASYS monotherapy for chronic hepatitis C is 180 µg (1.0
899 mL vial or 0.5 mL prefilled syringe) once weekly for 48 weeks by subcutaneous
900 administration in the abdomen or thigh.

901 PEGASYS and COPEGUS Combination Therapy

902 The recommended dose of PEGASYS when used in combination with ribavirin for
903 chronic hepatitis C is 180 µg (1.0 mL vial or 0.5 mL prefilled syringe) once weekly. The
904 recommended dose of COPEGUS and duration for PEGASYS/COPEGUS therapy is
905 based on viral genotype (see Table 7).

906 The daily dose of COPEGUS is 800 mg to 1200 mg administered orally in two divided
907 doses. The dose should be individualized to the patient depending on baseline disease
908 characteristics (e.g., genotype), response to therapy, and tolerability of the regimen.

909 Since COPEGUS absorption increases when administered with a meal, patients are
910 advised to take COPEGUS with food.

PEGASYS (peginterferon alfa-2a)

911 **Table 7 PEGASYS and COPEGUS Dosing Recommendations**

Genotype	PEGASYS Dose	COPEGUS Dose	Duration
Genotypes 1, 4	180 µg	<75 kg = 1000 mg	48 weeks
		≥75 kg = 1200 mg	48 weeks
Genotypes 2, 3	180 µg	800 mg	24 weeks

912 Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks (see Table 3).

913 Data on genotypes 5 and 6 are insufficient for dosing recommendations.

914

915 **CHC with HIV Coinfection**

916 **PEGASYS Monotherapy**

917 The recommended dose of PEGASYS monotherapy for chronic hepatitis C in patients
918 coinfecting with HIV is 180 µg (1.0 mL vial or 0.5 mL prefilled syringe) once weekly for
919 48 weeks by subcutaneous administration in the abdomen or thigh.

920 **PEGASYS/COPEGUS Combination Therapy**

921 The recommended dose when used in combination with ribavirin is PEGASYS 180 µg sc
922 once weekly and COPEGUS 800 mg po daily given in two divided doses for a total of 48
923 weeks, regardless of genotype.

924 Since COPEGUS absorption increases when administered with a meal, patients are
925 advised to take COPEGUS with food.

926 **Chronic Hepatitis B**

927 **PEGASYS Monotherapy**

928 The recommended dose of PEGASYS monotherapy for hepatitis B is 180 µg (1.0 mL
929 vial or 0.5 mL prefilled syringe) once weekly for 48 weeks by subcutaneous
930 administration in the abdomen or thigh.

931 **Dose Modifications**

932 **If severe adverse reactions or laboratory abnormalities develop during combination**
933 **COPEGUS/PEGASYS therapy, the dose should be modified or discontinued, if**
934 **appropriate, until the adverse reactions abate. If intolerance persists after dose**
935 **adjustment, COPEGUS/PEGASYS therapy should be discontinued.**

936 **PEGASYS**

937 **General**

938 When dose modification is required for moderate to severe adverse reactions (clinical
939 and/or laboratory), initial dose reduction to 135 µg (which is 0.75 mL for the vials or
940 adjustment to the corresponding graduation mark for the syringes) is generally adequate.
941 However, in some cases, dose reduction to 90 µg (which is 0.5 mL for the vials or
942 adjustment to the corresponding graduation mark for the syringes) may be needed.

PEGASYS (peginterferon alfa-2a)

943 Following improvement of the adverse reaction, re-escalation of the dose may be
 944 considered (see **WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS**).

945 Hematological

946 **Table 8 PEGASYS Hematological Dose Modification Guidelines**

Laboratory Values	Reduce PEGASYS Dose to:	Discontinue PEGASYS if:
ANC \geq 750/mm ³ ANC <750/mm ³	Maintain 180 μ g Reduce to 135 μ g	ANC <500/mm ³ , treatment should be suspended until ANC values return to more than 1000/mm ³ Reinstitute at 90 μ g and monitor ANC
Platelet \geq 50,000/mm ³ Platelet <50,000/mm ³	Maintain 180 μ g Reduce to 90 μ g	Platelet count <25,000/mm ³

947 Psychiatric: Depression

948 **Table 9 Guidelines for Modification or Discontinuation of PEGASYS**
 949 **and for Scheduling Visits for Patients with Depression**

Depression Severity	Initial Management (4-8 weeks)		Depression		
	Dose modification	Visit schedule	Remains stable	Improves	Worsens
Mild	No change	Evaluate once weekly by visit and/or phone	Continue weekly visit schedule	Resume normal visit schedule	(See moderate or severe depression)
Moderate	Decrease PEGASYS dose to 135 μ g (in some cases dose reduction to 90 μ g may be needed)	Evaluate once weekly (office visit at least every other week)	Consider psychiatric consultation. Continue reduced dosing	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose	(See severe depression)
Severe	Discontinue PEGASYS permanently	Obtain immediate psychiatric consultation	Psychiatric therapy necessary		

PEGASYS (peginterferon alfa-2a)

950 Renal Function

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

954 Liver Function

955 If ALT increases are progressive despite dose reduction or accompanied by increased
956 bilirubin or evidence of hepatic decompensation, therapy should be immediately
957 discontinued.

958 In chronic hepatitis C patients with progressive ALT increases above baseline values, the
959 dose of PEGASYS should be reduced to 135 µg and more frequent monitoring of liver
960 function should be performed. After PEGASYS dose reduction or withholding, therapy
961 can be resumed after ALT flares subside.

962 In chronic hepatitis B patients with elevations in ALT (>5 x ULN), more frequent
963 monitoring of liver function should be performed and consideration should be given to
964 either reducing the dose of PEGASYS to 135 µg or temporarily discontinuing treatment.
965 After PEGASYS dose reduction or withholding, therapy can be resumed after ALT flares
966 subside.

967 In patients with persistent, severe (ALT >10 times above the upper limit of normal)
968 hepatitis B flares, consideration should be given to discontinuation of treatment.

969 COPEGUS

970 **Table 10 COPEGUS Dosage Modification Guidelines**

Laboratory Values	Reduce Only COPEGUS Dose to 600 mg/day* if:	Discontinue COPEGUS if:
Hemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
Hemoglobin in patients with history of stable cardiac disease	≥2 g/dL decrease in hemoglobin during any 4 week period treatment	<12 g/dL despite 4 weeks at reduced dose

971 * One 200 mg tablet in the morning and two 200 mg tablets in the evening.

972

973 Once COPEGUS has been withheld due to a laboratory abnormality or clinical
974 manifestation, an attempt may be made to restart COPEGUS at 600 mg daily and further
975 increase the dose to 800 mg daily depending upon the physician's judgment. However, it
976 is not recommended that COPEGUS be increased to the original dose (1000 mg or
977 1200 mg).

PEGASYS (peginterferon alfa-2a)

978 Renal Impairment

979 COPEGUS should not be used in patients with creatinine clearance <50 mL/min (see
980 **CLINICAL PHARMACOLOGY, WARNINGS and COPEGUS Package Insert**).

981 HOW SUPPLIED

982 Single Dose Vial

983 Each PEGASYS (peginterferon alfa-2a) 180 µg single use, clear glass vial provides
984 1.0 mL containing 180 µg peginterferon alfa-2a for sc injection. Each package contains 1
985 vial (NDC 0004-0350-09).

986 Vials Monthly Convenience Pack

987 Four vials of PEGASYS (peginterferon alfa-2a), 180 µg single use, clear glass vials, in a
988 box with 4 syringes and 8 alcohol swabs (NDC 0004-0350-39). Each syringe is a 1 mL
989 (1 cc) volume syringe supplied with a 27-gauge, ½-inch needle with needle-stick
990 protection device.

991 Prefilled Syringes Monthly Convenience Pack

992 Four prefilled syringes of PEGASYS (peginterferon alfa-2a), 180 µg single use,
993 graduated, clear glass prefilled syringes, in a box with 4 needles and 4 alcohol swabs
994 (NDC 0004-0352-39). Each syringe is a 0.5 mL (½ cc) volume syringe supplied with a
995 27-gauge, ½-inch needle with needle-stick protection device.

996 Storage

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

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1003 MEDICATION GUIDE

1004 PEGASYS

1005 (peginterferon alfa-2a)

1006 Before you start taking PEGASYS (PEG-ah-sis), alone or in combination with
1007 COPEGUS (Co-PEG-UHS), please read this Medication Guide carefully. Read this
1008 Medication Guide each time you refill your prescription in case new information has
1009 been added and make sure the pharmacist has given you the medicine your healthcare
1010 provider prescribed for you. Reading the information in this Medication Guide does not
1011 take the place of talking with your healthcare provider.

1012 *If you are taking PEGASYS in combination with COPEGUS, you should also read the*
1013 *Medication Guide for COPEGUS (ribavirin, USP) Tablets.*

PEGASYS (peginterferon alfa-2a)

1014 What is the most important information I should know about PEGASYS 1015 therapy?

1016 PEGASYS, taken alone or in combination with COPEGUS, is a treatment for some
1017 people who are infected with hepatitis C virus. PEGASYS taken alone is a treatment for
1018 some people who are infected with the hepatitis B virus. However, PEGASYS and
1019 COPEGUS can have serious side effects that may cause death in rare cases. Before
1020 starting PEGASYS therapy, you should talk with your healthcare provider about the
1021 possible benefits and the possible side effects of treatment, to decide if either of these
1022 treatments is right for you. If you begin treatment you will need to see your healthcare
1023 provider regularly for examinations and blood tests to make sure your treatment is
1024 working and to check for side effects.

1025 The most serious possible side effects of PEGASYS taken alone or in combination with
1026 COPEGUS include:

1027 Risks to Pregnancy:

1028 **Taking PEGASYS in combination with COPEGUS tablets can cause death, serious
1029 birth defects or other harm to your unborn child. Therefore, if you are pregnant or
1030 your partner is pregnant or plans to become pregnant, do not take
1031 PEGASYS/COPEGUS combination therapy. Female patients and female partners
1032 of male patients being treated with PEGASYS/COPEGUS combination therapy
1033 must not become pregnant during treatment and for 6 months after treatment has
1034 stopped. During this time, you must have pregnancy tests that show you are not
1035 pregnant. You must also use two effective forms of birth control during therapy and
1036 for 6 months after stopping therapy. Male patients should use a condom with
1037 spermicide as one of the two forms.** You must use birth control even if you believe that
1038 you are not fertile or that your fertility is low. You should talk to your healthcare provider
1039 about birth control for you and your partner.

1040 **If you are pregnant, you or your male partner must not take PEGASYS/COPEGUS
1041 combination therapy. If you or your partner are being treated and you become
1042 pregnant either during treatment or within 6 months of stopping treatment, call
1043 your healthcare provider right away.**

1044 If you or a female sexual partner becomes pregnant, you should tell your healthcare
1045 provider. There is a Ribavirin Pregnancy Registry that collects information about
1046 pregnancy outcomes of female patients and female partners of male patients exposed to
1047 ribavirin. You or your healthcare provider are encouraged to contact the Registry at 1-
1048 800-593-2214.

1049 Mental health problems:

1050 PEGASYS may cause some patients to develop mood or behavioral problems. Signs of
1051 these problems include irritability (getting easily upset), depression (feeling low, feeling
1052 bad about yourself or feeling hopeless), and anxiety. Some patients may have aggressive
1053 behavior. Some patients may develop thoughts about ending their lives (suicidal
1054 thoughts) and may attempt to do so. A few patients have even ended their lives. Former
1055 drug addicts may fall back into drug addiction or overdose. You must tell your healthcare

PEGASYS (peginterferon alfa-2a)

1056 provider if you are being treated for a mental illness or have a history of mental illness or
1057 if you are or have ever been addicted to drugs or alcohol. Call your healthcare provider
1058 immediately if you develop any of these problems while on PEGASYS treatment.

1059 Blood problems:

1060 Many patients taking PEGASYS have had a drop in the number of their white blood cells
1061 and their platelets. If the numbers of these blood cells are too low, you could be at risk for
1062 serious infections or bleeding.

1063 COPEGUS causes a decrease in the number of your red blood cells (anemia). This can be
1064 dangerous, especially for patients who already have heart or circulatory (cardiovascular)
1065 problems. If you have or have ever had any cardiovascular problems, talk with your
1066 healthcare provider before taking the combination of PEGASYS and COPEGUS.

1067 Liver problems:

1068 Infrequently, some patients with hepatitis C and liver scarring can develop sudden severe
1069 worsening (failure) of their liver disease while taking PEGASYS. Patients infected with
1070 both the hepatitis C virus and HIV can have an increased chance of having liver failure
1071 during PEGASYS treatment.

1072 Some patients taking PEGASYS for hepatitis B have had a rise in a blood test that
1073 measures liver inflammation. If you have a rise in this blood test, your liver may need to
1074 be watched more closely with additional blood tests.

1075 Infections:

1076 Some patients taking interferon have had serious infections. Sometimes these infections
1077 have been fatal. If you develop a fever that does not go away or gets higher, call your
1078 healthcare provider right away. Your healthcare provider will need to examine you to rule
1079 out your having a serious infection.

1080 Body organ problems:

1081 Some patients may experience lung problems (such as difficulty breathing or pneumonia)
1082 and eye problems that can cause blurred vision or loss of your vision.

1083 Call your healthcare provider immediately if you develop any of these 1084 conditions:

- 1085 • **You become very depressed or think about suicide**
- 1086 • **You have severe chest pain**
- 1087 • **You have trouble breathing**
- 1088 • **You have a change in your vision**
- 1089 • **You become pregnant**
- 1090 • **You notice unusual bleeding or bruising**
- 1091 • **You have psoriasis (a skin disease) and it gets worse while taking PEGASYS**
- 1092 • **High fever or a fever that does not go away**
- 1093 • **You have severe stomach pain or lower back pain**
- 1094 • **Bloody diarrhea**
- 1095

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1096 *For more information on possible side effects with PEGASYS therapy, alone or in*
1097 *combination with COPEGUS, please read the section on “**What are the possible side***
1098 ***effects of PEGASYS, and PEGASYS taken with COPEGUS?” in this Medication***
1099 *Guide. You should also read the Medication Guide for COPEGUS tablets if you are*
1100 *taking that medicine with PEGASYS.*

1101 What is PEGASYS?

1102 PEGASYS is a drug used to treat adults who have a lasting (chronic) infection with
1103 hepatitis C virus or hepatitis B virus and who show signs that the virus is damaging the
1104 liver. Patients with hepatitis have the virus in their blood and in their liver. PEGASYS
1105 reduces the amount of hepatitis C virus in the body and helps the body's immune system
1106 fight the virus. The drug COPEGUS are tablets that may be taken with PEGASYS to help
1107 fight the virus infection. Do not take COPEGUS by itself.

1108 In some patients that have received PEGASYS treatment for approximately one year to
1109 treat hepatitis C, the amount of the hepatitis virus in the body was decreased to a level so
1110 low that it could not be measured by blood tests. After 3 months of therapy, your
1111 healthcare provider may ask you to have a blood test to help determine how you are
1112 responding to your treatment.

1113 It is not known if PEGASYS, used alone or in combination with COPEGUS, can cure
1114 hepatitis (permanently eliminate the virus) or if it can prevent liver failure or liver cancer
1115 that is caused by hepatitis infection.

1116 It is also not known if PEGASYS, alone or in combination with COPEGUS, will prevent
1117 one infected person from infecting another person with hepatitis.

1118 Who should not take PEGASYS, or PEGASYS with COPEGUS?

1119 Do not take PEGASYS or PEGASYS/COPEGUS therapy if you:

- 1120 • are pregnant, planning to get pregnant during treatment or during the 6 months after
1121 treatment or breast-feeding
- 1122 • are a male patient with a female sexual partner who is pregnant or plans to become
1123 pregnant at any time while you are being treated with COPEGUS or during the 6
1124 months after your treatment has ended
- 1125 • have hepatitis caused by your immune system attacking your liver (autoimmune
1126 hepatitis)
- 1127 • have unstable or severe liver disease
- 1128 • had an allergic reaction to another alpha interferon or are allergic to any of the
1129 ingredients in PEGASYS or COPEGUS tablets
- 1130 • Do not take PEGASYS, alone or in combination with COPEGUS, if you have
1131 abnormal red blood cells such as sickle-cell anemia or thalassemia major.
1132

1133 **If you have ever had any of the following conditions or serious medical**
1134 **problems, tell your healthcare provider before you start taking PEGASYS:**

- 1135 • History of or current severe mental illness (such as depression or anxiety)
- 1136 • History of drug or alcohol addiction or abuse

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- 1137 • History of heart disease or previous heart attack
- 1138 • History of cancer
- 1139 • Autoimmune disease (where the body's immune system attacks the body's own
- 1140 cells), such as psoriasis (a skin disease), systemic lupus erythematosus, rheumatoid
- 1141 arthritis
- 1142 • Kidney problems
- 1143 • Blood disorders
- 1144 • You take a medicine called theophylline
- 1145 • Diabetes (high blood sugar)
- 1146 • Problems with the thyroid gland
- 1147 • Liver problems, other than hepatitis C or hepatitis B
- 1148 • Colitis (an inflammation of the bowels)

1149

1150 You should tell your healthcare provider if you are taking or planning to take other
1151 prescription or nonprescription medicines or vitamin and mineral supplements or herbal
1152 medicines.

1153 If you have any questions about your health condition or about taking PEGASYS alone
1154 or in combination with COPEGUS, you should talk to your healthcare provider.

1155 **How should I take PEGASYS, or PEGASYS with COPEGUS?**

1156 PEGASYS is given by injection under the skin (subcutaneous injection). PEGASYS
1157 comes in two different forms (a liquid in a single use vial and a liquid in a prefilled
1158 syringe). Your healthcare provider will determine which is best for you. Your healthcare
1159 provider will also decide whether you will take PEGASYS alone or with COPEGUS.
1160 Your dose of PEGASYS is given as a single injection once per week. At some point, your
1161 healthcare provider may change your dose of PEGASYS or COPEGUS. Do not change
1162 your dose unless your healthcare provider tells you to change it. It is important that you
1163 take PEGASYS and COPEGUS exactly as your healthcare provider tells you. Once you
1164 start treatment with PEGASYS, do not switch to another brand of interferon without
1165 talking to your healthcare provider. Other interferons may not have the same effect on the
1166 treatment of your disease. Switching brands will also require a change in your dose.

1167 Take your prescribed dose of PEGASYS once a week, on the same day of each week and
1168 at approximately the same time. Your total dose of COPEGUS tablets should be divided
1169 so you take it twice a day with food (breakfast and dinner). Taking half your dose of
1170 COPEGUS in the morning and the other half at night will keep the medicine in your body
1171 at a steady level. Do not take more than your prescribed dose of PEGASYS or
1172 COPEGUS. **Be sure to read the Medication Guide for COPEGUS (ribavirin, USP)**
1173 **for complete instructions on how to take the COPEGUS tablets.**

1174 Your healthcare provider will train you and/or the person that will be giving you the
1175 PEGASYS injections on the proper way to give injections. Whether you give yourself the
1176 injection or another person gives the injection to you, it is important that you are
1177 comfortable with preparing and injecting a dose of PEGASYS, and you understand the
1178 instructions in "How do I inject PEGASYS?" **At the end of this guide there are**

PEGASYS (peginterferon alfa-2a)

1179 **detailed instructions on how to prepare and give yourself an injection of PEGASYS**
1180 **using the form your healthcare provider has prescribed for you.**

1181 If you miss a dose and you remember **within 2 days** of when you should have taken
1182 PEGASYS, give yourself an injection of PEGASYS as soon as you remember. Take your
1183 next dose on the day you would usually take it. If **more than 2 days** have passed, ask
1184 your healthcare provider what you should do. If you miss a dose of COPEGUS, take the
1185 missed dose as soon as you remember during the same day. Do not take 2 doses too close
1186 together in time. If it is late in the day, wait until the next day and go back on schedule.
1187 **Do not double the next dose.**

1188 If you take more than the prescribed amount of PEGASYS, call your healthcare provider
1189 right away. Your healthcare provider may want to examine you and take blood for
1190 testing.

1191 You must get regular blood tests to help your healthcare provider check how the
1192 treatment is working and to check for side effects.

1193 **What should I avoid while taking PEGASYS, or PEGASYS with COPEGUS?**

- 1194 • If you are pregnant do not start taking or continue taking COPEGUS in combination
1195 with PEGASYS. (See “**What is the most important information I should know**
1196 **about PEGASYS therapy? Risks to Pregnancy**”.)
- 1197 • Avoid becoming pregnant while taking PEGASYS, alone or in combination with
1198 COPEGUS. PEGASYS, alone or in combination with COPEGUS, may harm your
1199 unborn child (death or serious birth defects) or cause you to lose your baby
1200 (miscarry). (See “**What is the most important information I should know about**
1201 **PEGASYS therapy? Risks to Pregnancy**”.)
- 1202 • Do not breast-feed your baby while on PEGASYS, alone or in combination with
1203 COPEGUS.

1204 **What are the possible side effects of PEGASYS, and PEGASYS taken with** 1205 **COPEGUS?**

1206 Possible, serious side effects include:

- 1207 • **Risk to pregnancy, mental health problems including suicidal thoughts, blood**
1208 **problems, infections, and body organ problems:** See “*What is the most important*
1209 *information I should know about PEGASYS therapy?*” in this Medication Guide.
- 1210 • **Autoimmune problems:** Some patients may develop a disease where the body's own
1211 immune system begins to attack itself (autoimmune disease) while on PEGASYS
1212 therapy. These diseases can include psoriasis or thyroid problems. In some patients
1213 who already have an autoimmune disease, the disease may worsen while on
1214 PEGASYS therapy.
- 1215 • **Heart problems:** PEGASYS may cause some patients to experience chest pain, and
1216 very rarely a heart attack. Patients who already have heart disease could be at greatest
1217 risk. Tell your healthcare provider if you have or have had a heart problem in the past.
- 1218 • **Liver problems:** Some patients may develop worsening of liver function. Some of
1219 the symptoms may include stomach bloating, confusion, brown urine, and yellow
1220 eyes. Tell your healthcare provider immediately if any of these symptoms occur.

PEGASYS (peginterferon alfa-2a)

1221

1222 Common, but less serious, side effects include:

- 1223 • **Flu-like symptoms:** Most patients who take PEGASYS have flu-like symptoms that
1224 usually lessen after the first few weeks of treatment. Flu-like symptoms may include
1225 fever, chills, muscle aches, joint pain, and headaches. Taking pain and fever reducers
1226 such as acetaminophen or ibuprofen before you take PEGASYS can help with these
1227 symptoms. You can also try taking PEGASYS at night. You may be able to sleep
1228 through the symptoms.
- 1229 • **Extreme fatigue (tiredness):** Many patients may become extremely tired while on
1230 PEGASYS therapy.
- 1231 • **Upset stomach:** Nausea, taste changes, diarrhea, and loss of appetite occur
1232 commonly.
- 1233 • **Blood sugar problems:** Some patients may develop a problem with the way their
1234 body controls their blood sugar and may develop diabetes.
- 1235 • **Skin reactions:** Some patients may develop rash, dry or itchy skin, and redness and
1236 swelling at the site of injection.
- 1237 • **Hair thinning:** Temporary hair loss is not uncommon during treatment with
1238 PEGASYS.
- 1239 • **Trouble sleeping**

1240 These are not all of the side effects of PEGASYS, and PEGASYS taken with COPEGUS.
1241 Your healthcare provider or pharmacist can give you a more complete list.

1242 Talk to your healthcare provider if you are worried about side effects or find them very
1243 bothersome.

1244 **General advice about prescription medicines**

1245 Medicines are sometimes prescribed for purposes other than those listed in a Medication
1246 Guide. If you have any concerns or questions about PEGASYS, contact your healthcare
1247 provider. Do not use PEGASYS for a condition or person other than that for which it is
1248 prescribed. If you want to know more about PEGASYS, your healthcare provider or
1249 pharmacist will be able to provide you with detailed information that is written for health-
1250 care providers.

1251 If you are taking COPEGUS (ribavirin, USP) in combination with PEGASYS, also read
1252 the Medication Guide supplied with that medicine.

1253 Keep this and all drugs out of the reach of children.

1254 This Medication Guide has been approved by the US Food and Drug Administration.

1255 Revised: May 2005

PEGASYS (peginterferon alfa-2a)

1256 Medication Guide Appendix: Instructions for Preparing and Giving a Dose with a 1257 PEGASYS Prefilled Syringe

1258 How should I store PEGASYS Prefilled Syringes?

1259 PEGASYS must be stored in the refrigerator at a temperature of 2°C to 8°C (36°F to
1260 46°F). Do not leave PEGASYS outside of the refrigerator for more than 24 hours. Do not
1261 freeze PEGASYS. Keeping PEGASYS at temperatures outside the recommended range
1262 can destroy the medicine.

1263 Each PEGASYS prefilled syringe can only be used once. Discard after use.

1264 Do not shake the prefilled syringe of PEGASYS. If PEGASYS is shaken too hard, it will
1265 not work properly.

1266 Protect PEGASYS from light during storage.

1267 Keep this and all other medicines out of the reach of children.

1268 How do I prepare and inject PEGASYS?

1269 You should read through all of these directions and ask your healthcare provider for help
1270 if you have any questions before trying to give yourself an injection. It is important to
1271 follow these directions carefully. Talk to your healthcare provider if you have any
1272 questions about PEGASYS.

1273 Your healthcare provider may not want you to take all the medicine that comes in the
1274 prefilled syringe. To appropriately administer the dose that your healthcare provider tells
1275 you to take, you may have to get rid of some of the medicine before injecting the
1276 medicine.

1277 If you ever switch between using prefilled syringes and vials, talk to your healthcare
1278 provider about how much PEGASYS to use. Equal volumes of liquid from the prefilled
1279 syringes and the vials DO NOT contain the same amount of PEGASYS. If you switch
1280 between prefilled syringes and vials, you will have to adjust the volume of liquid that you
1281 use to give your injection. If you do not adjust this, you could accidentally take too much
1282 or too little of your medicine.

1283 If you are giving this injection to someone else, a healthcare provider must teach you how
1284 to avoid needle sticks. Being stuck by a used needle can pass diseases on to you.

1285 The prefilled syringes are used for injecting PEGASYS under the surface of the skin
1286 (subcutaneous).

1287

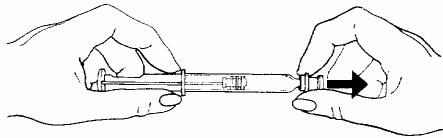
1288 1. Collect all the materials you will need before you start to give the injection:
1289

- 1290 • One PEGASYS prefilled syringe Monthly Convenience Pack containing an
1291 inner carton holding the PEGASYS prefilled syringe
- 1292 • A puncture-resistant container for cleaning up when you are finished
1293

1294 2. Open the convenience pack and look at the contents.

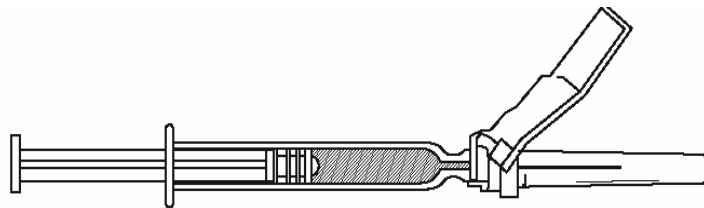
PEGASYS (peginterferon alfa-2a)

- 1295
- Each convenience pack has everything you need for the PEGASYS injection.
- 1296
- 4 single use syringes filled with medicine (should be colorless to light yellow)
- 1297
- 1298
- four 27-gauge, ½-inch needles with needle-stick protection device
- 1299
- 4 alcohol swabs
- 1300
- Do not use PEGASYS if:
- 1301
- the medicine is cloudy
- 1302
- the medicine has particles floating in it
- 1303
- the medicine is any color besides colorless to light yellow
- 1304
- the expiration date has passed
- 1305
3. Warm the refrigerated medicine by gently rolling it in the palms of your hands for
- 1306
- about one minute. Do not shake.
- 1307
4. Wash your hands with soap and warm water to prevent infection.
- 1308
5. Attachment of the needle to the PEGASYS prefilled syringe:
- 1309
- Remove the needle from its package. Do not remove the needle shield yet.
- 1310
- Keep the needle covered until just before you give the injection.
- 1311
- Remove and discard the rubber cap from the tip of the syringe barrel.
- 1312



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- 1314
- Put the needle onto the end of the syringe barrel so it fits tightly.
- 1315
- Here is a picture of the assembled syringe:
- 1316



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1318

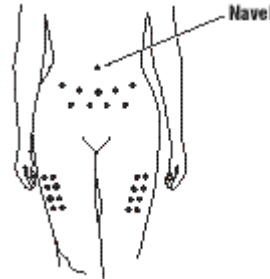
- 1319
- Keep the syringe in a horizontal position until ready for use.
- 1320
- If you need to set the syringe down, make sure the plastic shield covers the
- 1321
- needle. Never let the needle touch any surface.

1322

6. Decide where you will give the injection.

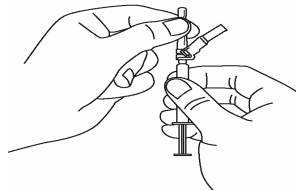
PEGASYS (peginterferon alfa-2a)

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- 1326
- Pick a place on your stomach or thigh (see the picture below). Avoid your navel and waistline. You should use a different place each time you give yourself an injection.



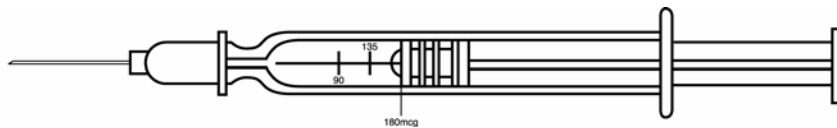
1327

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- 1335
7. Prepare your skin for the injection.
 - To minimize the discomfort from injections, you may want to gently tap the area where you plan to give yourself an injection.
 - Clean the area using the alcohol pad. Let the skin dry for 10 seconds.
 8. Uncover the needle.
 - Remove the plastic safety shield covering the needle. Do not remove the orange cap that is attached to the end of the syringe and above the needle that is the needle-stick protection device.



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- 1348
9. Remove air bubbles from the syringe.
 - Hold the syringe with the needle pointing up to the ceiling.
 - Using your thumb and finger, tap the syringe to bring air bubbles to the top.
 - Press the plunger in slightly to push air bubbles out of the syringe.
 - Your healthcare provider may not want you to take all the medicine that comes in the prefilled syringe.
 - To appropriately administer the dose that your healthcare provider tells you to take, you may have to get rid of some of the medicine before injecting the medicine.
 - The syringe has markings for 180 mcg, 135 mcg, and 90 mcg. Your healthcare provider will tell you which mark to use.



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- Once you know which mark to use, slowly and carefully press on the plunger rod of the syringe to push out medicine from the syringe. Keep pressing until

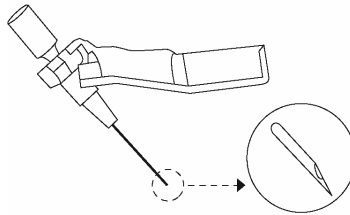
PEGASYS (peginterferon alfa-2a)

1353 the edge of the plunger stopper reaches the right mark on the side of the
1354 syringe.

1355 • Do not decrease or increase your dose of PEGASYS unless your healthcare
1356 provider tells you to.

1357 10. Give the injection of PEGASYS.

1358 • Position the point of the needle (the bevel) so it is facing up.



1359

1360 • Pinch a fold of skin on your stomach or thigh firmly with your thumb and
1361 forefinger.



1362

1363 • Hold the syringe like a pencil at a 45° to 90° angle to your skin. In one quick
1364 motion, insert the needle as far as it will go into the pinched area of skin. Pull
1365 the plunger of the syringe back very slightly. If blood comes into the syringe,
1366 the needle has entered a blood vessel. **Do not inject. Withdraw the needle
1367 and discard the syringe as outlined in step 11. Repeat the above steps
1368 with a new prefilled syringe and prepare a new site.**

1369 • If no blood appears, release your skin and slowly push the plunger all the way
1370 down so that you get all of your medicine.



1371

1372 • Pull out the needle at same angle you put it in.

1373 • Wipe the area with an alcohol swab.

1374 11. For safety reasons, before you dispose of the syringe and needle, place the free end of
1375 the orange cap on a flat surface and push down on it until it clicks and covers over the
1376 needle. Always place used syringes and needles in a puncture-resistant container
1377 immediately after use and never reuse them. Keep your disposal container out of the
1378 reach of children.

PEGASYS (peginterferon alfa-2a)

1379 How should I dispose of materials used to inject PEGASYS?

1380 There may be special state and local laws for disposal of used needles and syringes. Your
1381 healthcare provider or pharmacist should provide you with instructions on how to
1382 properly dispose of your used syringes and needles. Always follow these instructions.

1383 The instructions below should be used as a general guide for proper disposal:

- 1384 • The needles and syringes should never be reused.
- 1385 • Place all used needles and syringes in a puncture-proof disposable container that is
1386 available through your pharmacy or healthcare provider (Sharp's container).
- 1387 • DO NOT use glass or clear plastic containers for disposal of needles and syringes.
- 1388 • Dispose of the full container as instructed by your healthcare provider or pharmacist.

1389

1390 **DO NOT throw the container in your household trash. DO NOT recycle. Keep the**
1391 **container out of the reach of children.**

1392 Appendix revision date: January 2004

1393 Medication Guide Appendix: Instructions for Preparing and Giving a Dose with a 1394 **PEGASYS Vial**

1395 How should I store PEGASYS vials?

1396 PEGASYS must be stored in the refrigerator at a temperature of 2°C to 8°C (36°F to
1397 46°F). Do not leave PEGASYS outside of the refrigerator for more than 24 hours. Do not
1398 freeze PEGASYS. Keeping PEGASYS at temperatures outside the recommended range
1399 can destroy the medicine.

1400 Each PEGASYS vial can only be used once. Discard after use.

1401 Do not shake the vial of PEGASYS. If PEGASYS is shaken too hard, it will not work
1402 properly.

1403 Protect PEGASYS from light during storage.

1404 Keep this and all other medicines out of the reach of children.

1405 How do I inject PEGASYS?

1406 The following instructions will help you learn how to measure your dose and give
1407 yourself an injection of PEGASYS. You should read through all of these directions and
1408 ask your healthcare provider for help if you have any questions before trying to give
1409 yourself an injection. It is important to follow these directions carefully. Talk to your
1410 healthcare provider if you have any questions about PEGASYS.

1411 If you are giving an injection to someone else, a healthcare provider must teach you how
1412 to avoid needle sticks. Being stuck by a used needle can pass diseases on to you.

1413 1. Collect all the materials you will need before you start to give the injection:

- 1414 • One vial of PEGASYS
- 1415 • One syringe and needle
- 1416 • Several alcohol pads

PEGASYS (peginterferon alfa-2a)

- 1417 • A puncture-resistant container to dispose of the needle and syringe when you are
1418 finished
1419

1420 If you have received the PEGASYS Convenience Pack, it includes PEGASYS, safety
1421 syringes and needles with a needle-stick protection device attached, and alcohol swabs.

1422
1423 2. Check the date on the carton the PEGASYS comes in and make sure the expiration
1424 date has not passed, then remove a vial from the package and look at the medicine.

- 1425 • Do not use PEGASYS if:
1426 – the medicine is cloudy
1427 – the medicine has particles floating in it
1428 – the medicine is any color besides colorless to light yellow
1429 – the expiration date has passed

1430 3. Warm the refrigerated medicine by gently rolling it in the palms of your hands for
1431 about one minute. Do not shake.

1432 4. Wash your hands with soap and warm water to prevent infection.

1433 5. Take the vial of PEGASYS and flip off the plastic top covering the vial opening, and
1434 clean the rubber stopper on the top of the vial with a different alcohol pad.

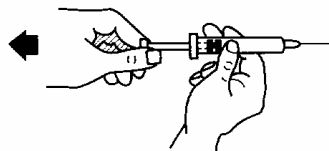


1435

1436 **If you are not sure how much medicine to use or which mark to use, STOP and call**
1437 **your healthcare provider right away.**

1438 6. Remove the needle and syringe from their packaging and attach the needle to the end
1439 of the syringe.

- 1440 • If you are using a syringe and needle supplied with the PEGASYS Convenience
1441 Pack, the needle is already attached to the syringe and it will have a needle-stick
1442 protection device attached. Remove the clear protective cap from the end of the
1443 needle. Do not remove the orange cap that is attached to the end of the syringe
1444 and above the needle that is the needle-stick protection device.
1445 • Pull the plunger back so the end of it is to the mark on the syringe barrel that
1446 matches the dose prescribed for you by your healthcare provider. This will pull air
1447 into the syringe barrel.

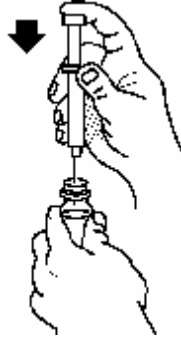


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- 1449 • Push the needle through the center of the stopper on the vial.

PEGASYS (peginterferon alfa-2a)

- 1450
- 1451
- Slowly inject all the air from the syringe into the air space above the solution. Do not inject air into the fluid.



1452

- 1453
- 1454
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- 1456
- Keep the needle inside the vial and turn both upside down. Hold the vial and syringe straight up. Slowly pull back on the plunger until the medicine is in the syringe up to the mark that matches your dose. Make sure the needle tip always stays in the medicine (not in the air space above it).



1457

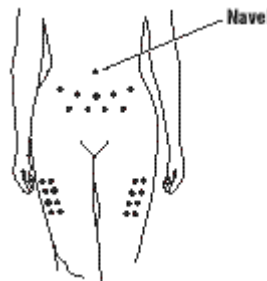
- 1458
- 1459
- 1460
- 1461
- 1462
- When the medicine is up to the right mark on the syringe barrel, take the syringe and needle out of the rubber stopper on the vial.
 - Keep the syringe pointing up until you are ready to use it.
 - If you need to set the syringe down, make sure that you never let the needle touch any surface.

1463 7. Remove air bubbles from the syringe.

- 1464
- 1465
- 1466
- Hold the syringe with the needle pointing up to the ceiling.
 - Using your thumb and finger, tap the syringe to bring air bubbles to the top.
 - Press the plunger in slightly to push air bubbles out of the syringe.

1467 8. Decide where you will give the injection.

- 1468
- 1469
- 1470
- Pick a place on your stomach or thigh (see the picture below). Avoid your navel and waistline. You should use a different place each time you give yourself an injection.



1471

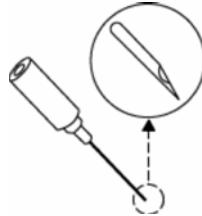
1472 9. Prepare your skin for the injection.

PEGASYS (peginterferon alfa-2a)

- 1473
- To minimize the discomfort from injections, you may want to gently tap the area
- 1474 where you plan to give yourself an injection.
- Clean the area using an alcohol pad. Let the skin dry for 10 seconds.
- 1475
- 1476

1477 10. Give the injection of PEGASYS.

- 1478
- Position the point of the needle (the bevel) so it is facing up.
- 1479



- 1480
- Pinch a fold of skin on your stomach or thigh firmly between your thumb and
- 1481 forefinger.
- 1482
- 1483



1484

- 1485
- Hold the syringe like a pencil at a 45° to 90° angle to your skin. In one quick
- 1486 motion, insert the needle as far as it will go into the pinched area of skin. Pull the
- 1487 plunger of the syringe back very slightly. If blood comes into the syringe, the
- 1488 needle has entered a blood vessel. **Do not inject. Withdraw the needle and**
- 1489 **discard the syringe as outlined in step 11. Repeat the above steps with a new**
- 1490 **vial and syringe and prepare a new site.**- If no blood appears, release your skin and slowly push the plunger all the way

1491 down so that you get all of your medicine.

1492

1493



1494

- 1495
- Pull out the needle at same angle you put it in. Wipe the area with an alcohol pad.

1496 11. For safety reasons, always place used syringes and needles in a puncture-resistant

1497 container immediately after use and never reuse them.

- 1498
- If you are using a syringe with a needle-stick protection device, before you
- 1499 dispose of the syringe and needle, place the free end of the orange cap on a flat
- 1500 surface and push down on it until it clicks and covers over the needle.

PEGASYS (peginterferon alfa-2a)

1501 **How should I dispose of materials used to inject PEGASYS?**

1502 There may be special state and local laws for disposal of used needles and syringes. Your
1503 healthcare provider or pharmacist should provide you with instructions on how to
1504 properly dispose of your used syringes and needles. Always follow these instructions.

1505 The instructions below should be used as a general guide for proper disposal:

- 1506 • The needles and syringes should never be reused.
- 1507 • Place all used needles and syringes in a puncture-proof disposable container that is
1508 available through your pharmacy or healthcare provider (Sharp's container).
- 1509 • DO NOT use glass or clear plastic containers for disposal of needles and syringes.
- 1510 • Dispose of the full container as instructed by your healthcare provider or pharmacist.

1511

1512 **DO NOT throw the container in your household trash. DO NOT recycle. Keep the**
1513 **container out of the reach of children.**

1514 Appendix revision date: January 2004



Pharmaceuticals

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