

**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 Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions.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  $6.0 \pm 0.5$ .

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  $6.0 \pm 0.5$ .

**39 CLINICAL PHARMACOLOGY****40 Pharmacodynamics**

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

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

**48 Pharmacokinetics**

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

52 Week 48 mean trough concentrations (16 ng/mL; range 4 to 28) at 168 hours post-dose  
53 are approximately 2-fold higher than week 1 mean trough concentrations (9 ng/mL; range  
54 0 to 15). Steady-state serum levels are reached within 5 to 8 weeks of once weekly  
55 dosing. The peak to trough ratio at week 48 is approximately 2. The mean systemic  
56 clearance in healthy subjects given PEGASYS was 94 mL/h, which is approximately  
57 100-fold lower than that for interferon alfa-2a (ROFERON®-A). The mean terminal half-  
58 life after sc dosing in patients with chronic hepatitis C was 160 hours (range 84 to 353  
59 hours) compared to 5 hours (range 3.7 to 8.5 hours) for ROFERON-A.

**60 Special Populations****61 Gender and Age**

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

**66 Pediatric Patients**

67 In a population pharmacokinetics study, 14 children 2 to 8 years of age with CHC  
68 received PEGASYS based on their body surface area (BSA of the child x  
69 180 µg/1.73m<sup>2</sup>). The clearance of PEGASYS in children was nearly 4-fold lower  
70 compared to the clearance reported in adults.

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

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### 79 Renal Dysfunction

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

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

### 87 Effect of Food on Absorption of Ribavirin

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

## 92 Drug Interactions

### 93 Nucleoside Analogues

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

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

### 104 Drugs Metabolized by Cytochrome P450

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

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

### 110 Methadone

111 The pharmacokinetics of concomitant administration of methadone and PEGASYS were  
112 evaluated in 24 PEGASYS naive chronic hepatitis C (CHC) patients (15 male, 9 female)  
113 who received 180 µg PEGASYS subcutaneously weekly. All patients were on stable  
114 methadone maintenance therapy (median dose 95 mg, range 30 mg to 150 mg) prior to  
115 receiving PEGASYS. Mean methadone PK parameters were 10% to 15% higher after 4  
116 weeks of PEGASYS treatment as compared to baseline (see **PRECAUTIONS: Drug**  
117 **Interactions**). Methadone did not significantly alter the PK of PEGASYS as compared to  
118 a PK study of 6 chronic hepatitis C patients not receiving methadone.

119 **CLINICAL STUDIES**

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

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

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

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

142 **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)

143 \*Percent difference between PEGASYS and ROFERON-A treatment.

144  
 145 Matched pre- and post-treatment liver biopsies were obtained in approximately 70% of  
 146 patients. Similar modest reductions in inflammation compared to baseline were observed  
 147 in all treatment groups.

148 Of the patients who did not demonstrate either undetectable HCV RNA or at least a  
 149  $2\log_{10}$  drop in HCV RNA titer from baseline by 12 weeks of PEGASYS 180 µg therapy,

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150 2% (3/156) achieved a sustained virologic response (see **DOSAGE AND**  
151 **ADMINISTRATION**).

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

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

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

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

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

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

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

178 In Study 5 (see **Table 3**), all patients received PEGASYS 180 µg sc qw and were  
179 randomized to treatment for either 24 or 48 weeks and to a COPEGUS dose of either  
180 800 mg or 1000 mg/1200 mg (for body weight <75 kg / ≥75 kg). Assignment to the four  
181 treatment arms was stratified by viral genotype and baseline HCV viral titer. Patients  
182 with genotype 1 and high viral titer (defined as >2 x 10<sup>6</sup> HCV RNA copies/mL serum)  
183 were preferentially assigned to treatment for 48 weeks.

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### 184 HCV Genotypes

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

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

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

194 **Table 3 Sustained Virologic Response as a Function of Genotype**  
195 **(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)
<b>Genotype 1</b>	29/101 (29%)	48/118 (41%)	99/250 (40%)	138/271 (51%)
<b>Genotypes 2, 3</b>	79/96 (82%)	116/144 (81%)	75/99 (76%)	117/153 (76%)
<b>Genotype 4</b>	0/5 (0%)	7/12 (58%)	5/8 (63%)	9/11 (82%)

196 \*1000 mg for body weight <75 kg; 1200 mg for body weight ≥75 kg.

### 197 Other Treatment Response Predictors

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

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

207 In studies 4 and 5, lack of early virologic response by 12 weeks (defined as HCV RNA  
208 undetectable or >2log<sub>10</sub> lower than baseline) was grounds for discontinuation of  
209 treatment. Of patients who lacked an early viral response by 12 weeks and completed a  
210 recommended course of therapy despite a protocol-defined option to discontinue therapy,  
211 5/39 (13%) achieved an SVR. Of patients who lacked an early viral response by 24  
212 weeks, 19 completed a full course of therapy and none achieved an SVR.

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

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

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

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

228 \*PEGASYS + COPEGUS vs. PEGASYS; PEGASYS + COPEGUS vs. ROFERON-A + COPEGUS p-  
229 value <0.0001 (Cochran-Mantel-Haenszel).

230  
231 Treatment response rates are lower in CHC/HIV patients with poor prognostic factors  
232 (including HCV genotype 1, HCV RNA >800,000 IU/mL, and cirrhosis) receiving  
233 pegylated interferon alpha therapy. Geographic region is not a prognostic factor for  
234 response. However, poor prognostic factors occur more frequently in the US population  
235 than in the non-US population.

236 Of the patients who did not demonstrate either undetectable HCV RNA or at least a  
237  $2\log_{10}$  reduction from baseline in HCV RNA titer by 12 weeks of PEGASYS and  
238 COPEGUS combination therapy, 2% (2/85) achieved an SVR.

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

### 242 **Chronic Hepatitis B Studies 7 and 8: PEGASYS Monotherapy**

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

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

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

257 The results observed in the PEGASYS and lamivudine monotherapy groups are shown in  
 258 **Table 5**.

259 **Table 5** Percentage of Patients with Serological, Virological,  
 260 **Biochemical, and Histological Response**

	Study 7 HBeAg positive			Study 8 HBeAg negative		
	Lamivudine N = 272		PEGASYS N = 271	Lamivudine N = 181		PEGASYS N = 177
	EOT <sup>1</sup>	EOF <sup>2</sup>	EOF <sup>2</sup>	EOT <sup>1</sup>	EOF <sup>2</sup>	EOF <sup>2</sup>
HBeAg Seroconversion (%)	20	19*	32*	NA	NA	NA
HBV DNA Response (%) <sup>3</sup>	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 (%) <sup>4</sup>	ND	40	41	ND	41	48
Changes in Ishak fibrosis score compared to baseline (%):						
- Improved <sup>5</sup>	ND	32	25	ND	31	32
- Unchanged		20	25		23	30
- Worsened <sup>5</sup>		16	26		15	19

261 <sup>1</sup>End of Treatment (week 48)

262 <sup>2</sup>End of follow-up – 24 weeks post-treatment (week 72)

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263 <sup>3</sup><100,000 copies/mL for HBeAg positive and <20,000 copies/mL for HBeAg negative patients  
264 <sup>4</sup>≥2 point decrease in Ishak necro-inflammatory score from baseline with no worsening of the Ishak fibrosis  
265 score. Not all patients provided both initial and end of follow-up biopsies (missing biopsy rates: 19% to  
266 24% in the PEGASYS and 31% to 32% in the Lamivudine arms)  
267 <sup>5</sup>Change of 1 point or more in Ishak fibrosis score  
268 \*p<0.001; \*\*p<0.01; \*\*\*p=0.012 (primary efficacy endpoints Cochran-Mantel-Haenszel test comparisons  
269 of PEGASYS to Lamivudine)  
270  
271 PEGASYS co-administered with lamivudine did not result in any additional sustained  
272 response when compared to PEGASYS monotherapy.  
  
273 Conclusions regarding comparative efficacy of PEGASYS and lamivudine treatment  
274 based upon the end of follow-up results are limited by the different mechanisms of action  
275 of the two compounds. Most treatment effects of lamivudine are unlikely to persist 24  
276 weeks after therapy is withdrawn.

### 277 INDICATIONS AND USAGE

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

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

### 288 CONTRAINDICATIONS

289 PEGASYS is contraindicated in patients with:

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

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

299 PEGASYS and COPEGUS combination therapy is additionally contraindicated in:

- 300 • Patients with known hypersensitivity to COPEGUS or to any component of the tablet

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- 301 • Women who are pregnant
- 302 • Men whose female partners are pregnant
- 303 • Patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)

### 304 **WARNINGS**

#### 305 **General**

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

#### 309 **Neuropsychiatric**

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

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

#### 322 **Infections**

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

#### 329 **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**).

335 PEGASYS and COPEGUS should be used with caution in patients with baseline  
336 neutrophil counts  $<1500$  cells/mm<sup>3</sup>, with baseline platelet counts  $<90,000$  cells/mm<sup>3</sup> 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**).

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340 Severe neutropenia and thrombocytopenia occur with a greater incidence in HIV  
341 coinfecting patients than monoinfected 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 **Cerebrovascular Disorders**

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

### 357 **Hepatic Failure and Hepatitis Exacerbations**

358 Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic  
359 decompensation and death when treated with alpha interferons, including PEGASYS.  
360 Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy  
361 (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk  
362 for the development of hepatic decompensation compared to patients not receiving  
363 HAART. In Study 6, among 129 CHC/HIV cirrhotic patients receiving HAART, 14  
364 (11%) of these patients across all treatment arms developed hepatic decompensation  
365 resulting in 6 deaths. All 14 patients were on NRTIs, including stavudine, didanosine,  
366 abacavir, zidovudine, and lamivudine. These small numbers of patients do not permit  
367 discrimination between specific NRTIs for the associated risk. During treatment,  
368 patients' clinical status and hepatic function should be closely monitored, and PEGASYS  
369 treatment should be immediately discontinued if decompensation (Child-Pugh score  $\geq 6$ )  
370 is observed (see **CONTRAINDICATIONS**).

371 Exacerbations of hepatitis during hepatitis B therapy are not uncommon and are  
372 characterized by transient and potentially severe increases in serum ALT. Chronic  
373 hepatitis B patients experienced transient acute exacerbations (flares) of hepatitis B (ALT  
374 elevation  $>10$ -fold higher than the upper limit of normal) during PEGASYS treatment  
375 (12% and 18%) and post-treatment (7% and 12%) in HBeAg negative and HBeAg  
376 positive patients, respectively. Marked transaminase flares while on PEGASYS therapy  
377 have been accompanied by other liver test abnormalities. Patients experiencing ALT  
378 flares should receive more frequent monitoring of liver function. PEGASYS dose  
379 reduction should be considered in patients experiencing transaminase flares. If ALT  
380 increases are progressive despite reduction of PEGASYS dose or are accompanied by  
381 increased bilirubin or evidence of hepatic decompensation, PEGASYS should be

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382 immediately discontinued (see **ADVERSE REACTIONS: Chronic Hepatitis B** and  
383 **DOSAGE AND ADMINISTRATION: Dose Modifications**).

### 384 **Hypersensitivity**

385 Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction,  
386 and anaphylaxis) have been rarely observed during alpha interferon and ribavirin therapy.  
387 If such reaction occurs, therapy with PEGASYS and COPEGUS should be discontinued  
388 and appropriate medical therapy immediately instituted. Serious skin reactions including  
389 vesiculobullous eruptions, reactions in the spectrum of Stevens Johnson Syndrome  
390 (erythema multiforme major) with varying degrees of skin and mucosal involvement and  
391 exfoliative dermatitis (erythroderma) have been rarely reported in patients receiving  
392 PEGASYS with and without ribavirin. Patients developing signs or symptoms of severe  
393 skin reactions must discontinue therapy (see **ADVERSE REACTIONS: Postmarketing**  
394 **Experience**).

### 395 **Endocrine Disorders**

396 PEGASYS causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia,  
397 hypoglycemia, and diabetes mellitus have been observed to develop in patients treated  
398 with PEGASYS. Patients with these conditions at baseline who cannot be effectively  
399 treated by medication should not begin PEGASYS therapy. Patients who develop these  
400 conditions during treatment and cannot be controlled with medication may require  
401 discontinuation of PEGASYS therapy.

### 402 **Autoimmune Disorders**

403 Development or exacerbation of autoimmune disorders including myositis, hepatitis,  
404 thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, psoriasis,  
405 rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus  
406 have been reported in patients receiving alpha interferon. PEGASYS should be used with  
407 caution in patients with autoimmune disorders.

### 408 **Pulmonary Disorders**

409 Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial  
410 pneumonitis, pulmonary hypertension and sarcoidosis, some resulting in respiratory  
411 failure and/or patient deaths, may be induced or aggravated by PEGASYS or alpha  
412 interferon therapy. Recurrence of respiratory failure has been observed with interferon  
413 rechallenge. PEGASYS combination treatment should be suspended in patients who  
414 develop pulmonary infiltrates or pulmonary function impairment. Patients who resume  
415 interferon treatment should be closely monitored.

### 416 **Colitis**

417 Ulcerative and hemorrhagic/ischemic colitis, sometimes fatal, have been observed within  
418 12 weeks of starting alpha interferon treatment. Abdominal pain, bloody diarrhea, and  
419 fever are the typical manifestations of colitis. PEGASYS should be discontinued  
420 immediately if these symptoms develop. The colitis usually resolves within 1 to 3 weeks  
421 of discontinuation of alpha interferon.

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### 422 **Pancreatitis**

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

### 427 **Ophthalmologic Disorders**

428 Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein  
429 thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema and  
430 serous retinal detachment are induced or aggravated by treatment with PEGASYS or  
431 other alpha interferons. All patients should receive an eye examination at baseline.  
432 Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive  
433 retinopathy) should receive periodic ophthalmologic exams during interferon alpha  
434 treatment. Any patient who develops ocular symptoms should receive a prompt and  
435 complete eye examination. PEGASYS treatment should be discontinued in patients who  
436 develop new or worsening ophthalmologic disorders.

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

438 **Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care**  
439 **must be taken to avoid pregnancy in female patients and in female partners of male**  
440 **patients taking PEGASYS and COPEGUS combination therapy. COPEGUS**  
441 **THERAPY SHOULD NOT BE STARTED UNLESS A REPORT OF A**  
442 **NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY**  
443 **PRIOR TO INITIATION OF THERAPY. Women of childbearing potential and**  
444 **men must use two forms of effective contraception during treatment and for at least**  
445 **6 months after treatment has concluded. Routine monthly pregnancy tests must be**  
446 **performed during this time (see [BOXED WARNING](#), [CONTRAINDICATIONS](#),**  
447 **[PRECAUTIONS: Information for Patients](#), and COPEGUS Package Insert).**

### 448 **Anemia**

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

458 Fatal and nonfatal myocardial infarctions have been reported in patients with anemia  
459 caused by ribavirin. Patients should be assessed for underlying cardiac disease before  
460 initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have  
461 electrocardiograms administered before treatment, and should be appropriately monitored  
462 during therapy. If there is any deterioration of cardiovascular status, therapy should be  
463 suspended or discontinued (see [DOSAGE AND ADMINISTRATION: COPEGUS](#)  
464 [Dosage Modification Guidelines](#)). Because cardiac disease may be worsened by drug-

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465 induced anemia, patients with a history of significant or unstable cardiac disease should  
466 not use COPEGUS (see **COPEGUS Package Insert**).

### 467 **Renal**

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

### 471 **Peripheral Neuropathy**

472 Peripheral neuropathy has been reported when alpha interferons were given in  
473 combination with telbivudine. In one clinical trial, an increased risk and severity of  
474 peripheral neuropathy was observed with the combination use of telbivudine and  
475 pegylated interferon-alfa 2a as compared to telbivudine alone. The safety and efficacy of  
476 telbivudine in combination with interferons for the treatment of chronic hepatitis B has  
477 not been demonstrated.

## 478 **PRECAUTIONS**

### 479 **General**

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

- 482 • Patients who have failed alpha interferon treatment with or without ribavirin
- 483 • Liver or other organ transplant recipients
- 484 • Hepatitis B patients coinfecting with HCV or HIV
- 485 • Hepatitis C patients coinfecting with HBV or coinfecting with HIV with a CD4+ cell  
486 count <100 cells/ $\mu$ L

487  
488 Caution should be exercised in initiating treatment in any patient with baseline risk of  
489 severe anemia (e.g., spherocytosis, history of GI bleeding).

### 490 **Renal Impairment**

491 A 25% to 45% higher exposure to PEGASYS is seen in subjects undergoing  
492 hemodialysis. In patients with impaired renal function, signs and symptoms of interferon  
493 toxicity should be closely monitored. Doses of PEGASYS should be adjusted  
494 accordingly. PEGASYS should be used with caution in patients with creatinine clearance  
495 <50 mL/min (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

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

### 498 **Information for Patients**

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

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503 PEGASYS and COPEGUS combination therapy must not be used by women who are  
504 pregnant or by men whose female partners are pregnant. COPEGUS therapy should not  
505 be initiated until a report of a negative pregnancy test has been obtained immediately  
506 before starting therapy. Female patients of childbearing potential and male patients with  
507 female partners of childbearing potential must be advised of the teratogenic/embryocidal  
508 risks and must be instructed to practice effective contraception during COPEGUS therapy  
509 and for 6 months post-therapy. Patients should be advised to notify the healthcare  
510 provider immediately in the event of a pregnancy (see **CONTRAINDICATIONS** and  
511 **WARNINGS**).

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

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

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

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

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

### 533 **Laboratory Tests**

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

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

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

547 • Platelet count  $\geq 90,000$  cells/mm<sup>3</sup> (as low as 75,000 cells/mm<sup>3</sup> in HCV patients with  
548 cirrhosis or 70,000 cells/mm<sup>3</sup> in patients with CHC and HIV)

549 • Absolute neutrophil count (ANC)  $\geq 1500$  cells/mm<sup>3</sup>

550 • Serum creatinine concentration  $< 1.5$  x upper limit of normal

551 • TSH and T<sub>4</sub> within normal limits or adequately controlled thyroid function

552 • CD4+ cell count  $\geq 200$  cells/ $\mu$ L or CD4+ cell count  $\geq 100$  cells/ $\mu$ L but  $< 200$  cells/ $\mu$ L  
553 and HIV-1 RNA  $< 5000$  copies/mL in patients coinfecting with HIV

554 • Hemoglobin  $\geq 12$  g/dL for women and  $\geq 13$  g/dL for men in CHC monoinfected  
555 patients

556 • Hemoglobin  $\geq 11$  g/dL for women and  $\geq 12$  g/dL for men in patients with CHC and  
557 HIV

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

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

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

571 Unlike hepatitis C, during hepatitis B therapy and follow up, transient elevations in ALT  
572 of 5 to 10 x ULN were observed in 25% and 27% and of  $> 10$  x ULN were observed in  
573 12% and 18%, of HBeAg negative and HBeAg positive patients, respectively. These  
574 ALT elevations have been accompanied by other liver test abnormalities (see  
575 **WARNINGS: Hepatic Failure and Hepatitis Exacerbations** and **DOSAGE AND**  
576 **ADMINISTRATION: Dose Modifications**).

### 577 **Drug Interactions**

578 Theophylline

579 Treatment with PEGASYS once weekly for 4 weeks in healthy subjects was associated  
580 with an inhibition of P450 1A2 and a 25% increase in theophylline AUC. Theophylline  
581 serum levels should be monitored and appropriate dose adjustments considered for

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582 patients given both theophylline and PEGASYS (see **CLINICAL PHARMACOLOGY:**  
583 **Drug Interactions**).

### 584 Methadone

585 In a PK study of HCV patients concomitantly receiving methadone, treatment with  
586 PEGASYS once weekly for 4 weeks was associated with methadone levels that were  
587 10% to 15% higher than at baseline (see **CLINICAL PHARMACOLOGY: Drug**  
588 **Interactions**). The clinical significance of this finding is unknown; however, patients  
589 should be monitored for the signs and symptoms of methadone toxicity.

### 590 Nucleoside Analogues

#### 591 *NRTIs*

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

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

#### 601 *Didanosine*

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

#### 606 *Zidovudine*

607 In Study 6, patients who were administered zidovudine in combination with  
608 PEGASYS/COPEGUS developed severe neutropenia (ANC <500) and severe anemia  
609 (hemoglobin <8 g/dL) more frequently than similar patients not receiving zidovudine  
610 (neutropenia 15% vs. 9%) (anemia 5% vs. 1%). Discontinuation of zidovudine should be  
611 considered as medically appropriate. Dose reduction or discontinuation of PEGASYS,  
612 COPEGUS or both should also be considered if worsening clinical toxicities are  
613 observed, including hepatic decompensation (e.g., Child-Pugh > 6).

#### 614 *Lamivudine, Stavudine, and Zidovudine*

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

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### 620 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### 621 Carcinogenesis

622 PEGASYS has not been tested for its carcinogenic potential.

#### 623 Mutagenesis

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

#### 627 *Use with Ribavirin*

628 Ribavirin is genotoxic and mutagenic. The carcinogenic potential of ribavirin has not  
629 been fully determined. In a p53 (+/-) mouse carcinogenicity study at doses up to the  
630 maximum tolerated dose of 100 mg/kg/day ribavirin was not oncogenic. However, on a  
631 body surface area basis, this dose was 0.5 times maximum recommended human 24-hour  
632 dose of ribavirin. A study in rats to assess the carcinogenic potential of ribavirin is  
633 ongoing (see **COPEGUS Package Insert**).

#### 634 Impairment of Fertility

635 PEGASYS may impair fertility in women. Prolonged menstrual cycles and/or  
636 amenorrhea were observed in female cynomolgus monkeys given sc injections of  
637 600 µg/kg/dose (7200 µg/m<sup>2</sup>/dose) of PEGASYS every other day for one month, at  
638 approximately 180 times the recommended weekly human dose for a 60 kg person (based  
639 on body surface area). Menstrual cycle irregularities were accompanied by both a  
640 decrease and delay in the peak 17β-estradiol and progesterone levels following  
641 administration of PEGASYS to female monkeys. A return to normal menstrual rhythm  
642 followed cessation of treatment. Every other day dosing with 100 µg/kg (1200 µg/m<sup>2</sup>)  
643 PEGASYS (equivalent to approximately 30 times the recommended human dose) had no  
644 effects on cycle duration or reproductive hormone status.

645 The effects of PEGASYS on male fertility have not been studied. However, no adverse  
646 effects on fertility were observed in male Rhesus monkeys treated with non-pegylated  
647 interferon alfa-2a for 5 months at doses up to 25 x 10<sup>6</sup> IU/kg/day.

#### 648 *Use with Ribavirin*

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

### 651 **Pregnancy**

#### 652 Pregnancy: Category C

653 PEGASYS has not been studied for its teratogenic effect. Non-pegylated interferon alfa-  
654 2a treatment of pregnant Rhesus monkeys at approximately 20 to 500 times the human  
655 weekly dose resulted in a statistically significant increase in abortions. No teratogenic  
656 effects were seen in the offspring delivered at term. PEGASYS should be assumed to  
657 have abortifacient potential. There are no adequate and well-controlled studies of  
658 PEGASYS in pregnant women. PEGASYS is to be used during pregnancy only if the  
659 potential benefit justifies the potential risk to the fetus. PEGASYS is recommended for

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660 use in women of childbearing potential only when they are using effective contraception  
661 during therapy.

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

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

#### 667 *Ribavirin Pregnancy Registry*

668 A Ribavirin Pregnancy Registry has been established to monitor maternal and fetal  
669 outcomes of pregnancies of female patients and female partners of male patients exposed  
670 to ribavirin during treatment and for 6 months following cessation of treatment.  
671 Healthcare providers and patients are encouraged to report such cases by calling 1-800-  
672 593-2214.

### 673 **Nursing Mothers**

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

### 679 **Pediatric Use**

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

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

### 685 **Geriatric Use**

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

### 698 **ADVERSE REACTIONS**

699 PEGASYS alone or in combination with COPEGUS causes a broad variety of serious  
700 adverse reactions (see **BOXED WARNING** and **WARNINGS**). The most common life-

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701 threatening or fatal events induced or aggravated by PEGASYS and COPEGUS were  
702 depression, suicide, relapse of drug abuse/overdose, and bacterial infections, each  
703 occurring at a frequency of <1%. Hepatic decompensation occurred in 2% (10/574) of  
704 CHC/HIV patients (see **WARNINGS: Hepatic Failure and Hepatitis Exacerbations**).

705 In all hepatitis C studies, one or more serious adverse reactions occurred in 10% of CHC  
706 monoinfected patients and in 19% of CHC/HIV patients receiving PEGASYS alone or in  
707 combination with COPEGUS. The most common serious adverse event (3% in CHC and  
708 5% in CHC/HIV) was bacterial infection (e.g., sepsis, osteomyelitis, endocarditis,  
709 pyelonephritis, pneumonia). Other SAEs occurred at a frequency of <1% and included:  
710 suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose,  
711 angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus,  
712 autoimmune phenomena (e.g., hyperthyroidism, hypothyroidism, sarcoidosis, systemic  
713 lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic  
714 ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism,  
715 coma, myositis, cerebral hemorrhage, thrombotic thrombocytopenic purpura, psychotic  
716 disorder, and hallucination.

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

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

728 Overall 39% of patients with CHC or CHC/HIV required modification of PEGASYS  
729 and/or COPEGUS therapy. The most common reason for dose modification of  
730 PEGASYS in CHC and CHC/HIV patients was for laboratory abnormalities, neutropenia  
731 (20% and 27%, respectively) and thrombocytopenia (4% and 6%, respectively). The most  
732 common reason for dose modification of COPEGUS in CHC and CHC/HIV patients was  
733 anemia (22% and 16%, respectively).

734 PEGASYS dose was reduced in 12% of patients receiving 1000 mg to 1200 mg  
735 COPEGUS for 48 weeks and in 7% of patients receiving 800 mg COPEGUS for 24  
736 weeks. COPEGUS dose was reduced in 21% of patients receiving 1000 mg to 1200 mg  
737 COPEGUS for 48 weeks and in 12% of patients receiving 800 mg COPEGUS for 24  
738 weeks.

739 Chronic hepatitis C monoinfected patients treated for 24 weeks with PEGASYS and 800  
740 mg COPEGUS were observed to have lower incidence of serious adverse events (3% vs.  
741 10%), Hgb <10 g/dL (3% vs. 15%), dose modification of PEGASYS (30% vs. 36%) and  
742 COPEGUS (19% vs. 38%) and of withdrawal from treatment (5% vs. 15%) compared to  
743 patients treated for 48 weeks with PEGASYS and 1000 mg or 1200 mg COPEGUS. On

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744 the other hand the overall incidence of adverse events appeared to be similar in the two  
745 treatment groups.

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

751 **Table 6 Adverse Reactions Occurring in ≥5% of Patients in Chronic**  
752 **Hepatitis C Clinical Trials (Pooled Studies 1, 2, 3, and**  
753 **Study 4)**

Body System	CHC Monotherapy (Pooled Studies 1-3)		CHC Combination Therapy Study 4	
	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
	%	%	%	%
<b>Application Site Disorders</b>				
Injection site reaction	22	18	23	16
<b>Endocrine Disorders</b>				
Hypothyroidism	3	2	4	5
<b>Flu-like Symptoms and Signs</b>				
Fatigue/Asthenia	56	57	65	68
Pyrexia	37	41	41	55
Rigors	35	44	25	37
Pain	11	12	10	9
<b>Gastrointestinal</b>				
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

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	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
	%	%	%	%
<b>Hematologic‡</b>				
Lymphopenia	3	5	14	12
Anemia	2	1	11	11
Neutropenia	21	8	27	8
Thrombocytopenia	5	2	5	<1
<b>Metabolic and Nutritional</b>				
Anorexia	17	17	24	26
Weight decrease	4	3	10	10
<b>Musculoskeletal, Connective Tissue and Bone</b>				
Myalgia	37	38	40	49
Arthralgia	28	29	22	23
Back pain	9	10	5	5
<b>Neurological</b>				
Headache	54	58	43	49
Dizziness (excluding vertigo)	16	12	14	14
Memory impairment	5	4	6	5
<b>Resistance Mechanism Disorders</b>				
Overall	10	6	12	10

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	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
	%	%	%	%
<b>Psychiatric</b>				
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
<b>Respiratory, Thoracic and Mediastinal</b>				
Dyspnea	4	2	13	14
Cough	4	3	10	7
Dyspnea exertional	<1	<1	4	7
<b>Skin and Subcutaneous Tissue</b>				
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
<b>Visual Disorders</b>				
Vision blurred	4	2	5	2

754

† Pooled studies 1, 2, and 3

755

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

756

\*\*Study 4

757

‡ Severe hematologic abnormalities (lymphocyte <0.5 x 10<sup>9</sup>/L; hemoglobin <10 g/dL;

758

neutrophil <0.75 x 10<sup>9</sup>/L; platelet <50 x 10<sup>9</sup>/L).

759

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### 760 **CHC With HIV Coinfection**

761 The adverse event profile of coinfecting patients treated with PEGASYS and COPEGUS  
762 in Study 6 was generally similar to that shown for monoinfected patients in Study 4  
763 (Table 6). Events occurring more frequently in coinfecting patients were neutropenia  
764 (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%), and mood  
765 alteration (9%).

### 766 **Chronic Hepatitis B**

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

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

775 The most commonly observed adverse reactions were pyrexia (54% vs. 4%), headache  
776 (27% vs. 9%), fatigue (24% vs. 10%), myalgia (26% vs. 4%), alopecia (18% vs. 2%), and  
777 anorexia (16% vs. 3%) in the PEGASYS and lamivudine groups respectively.

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

### 782 **Laboratory Test Values**

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

#### 785 **Neutrophils**

786 In the hepatitis C studies, decreases in neutrophil count below normal were observed in  
787 95% of all patients treated with PEGASYS either alone or in combination with  
788 COPEGUS. Severe potentially life-threatening neutropenia ( $ANC < 0.5 \times 10^9/L$ ) occurred  
789 in 5% of CHC patients and 12% of CHC/HIV patients receiving PEGASYS either alone  
790 or in combination with COPEGUS. Modification of PEGASYS dose for neutropenia  
791 occurred in 17% of patients receiving PEGASYS monotherapy and 22% of patients  
792 receiving PEGASYS/COPEGUS combination therapy. In the CHC/HIV patients 27%  
793 required modification of interferon dosage for neutropenia. Two percent of patients with  
794 CHC and 10% of patients with CHC/HIV required permanent reductions of PEGASYS  
795 dosage and <1% required permanent discontinuation. Median neutrophil counts return to  
796 pre-treatment levels 4 weeks after cessation of therapy (see **DOSAGE AND  
797 ADMINISTRATION: Dose Modifications**).

#### 798 **Lymphocytes**

799 Decreases in lymphocyte count are induced by interferon alpha therapy. PEGASYS plus  
800 COPEGUS combination therapy induced decreases in median total lymphocyte counts

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801 (56% in CHC and 40% in CHC/HIV, with median decrease of 1170 cells/mm<sup>3</sup> in CHC  
802 and 800 cells/mm<sup>3</sup> in CHC/HIV). In the hepatitis C studies, lymphopenia was observed  
803 during both monotherapy (81%) and combination therapy with PEGASYS and  
804 COPEGUS (91%). Severe lymphopenia (<0.5 x 10<sup>9</sup>/L) occurred in approximately 5% of  
805 all monotherapy patients and 14% of all combination PEGASYS and COPEGUS therapy  
806 recipients. Dose adjustments were not required by protocol. The clinical significance of  
807 the lymphopenia is not known.

808 In CHC with HIV coinfection, CD4 counts decreased by 29% from baseline (median  
809 decrease of 137 cells/mm<sup>3</sup>) and CD8 counts decreased by 44% from baseline (median  
810 decrease of 389 cells/mm<sup>3</sup>) in the PEGASYS plus COPEGUS combination therapy arm.  
811 Median lymphocyte CD4 and CD8 counts return to pre-treatment levels after 4 to 12  
812 weeks of the cessation of therapy. CD4% did not decrease during treatment.

### 813 Platelets

814 In the hepatitis C studies, platelet counts decreased in 52% of CHC patients and 51% of  
815 CHC/HIV patients treated with PEGASYS alone (respectively median decrease of 41%  
816 and 35% from baseline), and in 33% of CHC patients and 47% of CHC/HIV patients  
817 receiving combination therapy with COPEGUS (median decrease of 30% from baseline).  
818 Moderate to severe thrombocytopenia (<50,000/mm<sup>3</sup>) was observed in 4% of CHC and  
819 8% of CHC/HIV patients. Median platelet counts return to pre-treatment levels 4 weeks  
820 after the cessation of therapy.

### 821 Hemoglobin

822 In the hepatitis C studies, the hemoglobin concentration decreased below 12 g/dL in 17%  
823 (median Hgb reduction of 2.2 g/dL) of monotherapy and 52% (median Hgb reduction of  
824 3.7 g/dL) of combination therapy patients. Severe anemia (Hgb <10 g/dL) was  
825 encountered in 13% of all patients receiving combination therapy and in 2% of CHC  
826 patients and 8% of CHC/HIV patients receiving PEGASYS monotherapy. Dose  
827 modification for anemia in COPEGUS recipients treated for 48 weeks occurred in 22% of  
828 CHC patients and 16% of CHC/HIV patients (see **DOSAGE AND**  
829 **ADMINISTRATION: Dose Modifications**).

### 830 Triglycerides

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

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

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### 839 ALT Elevations

#### 840 *Chronic Hepatitis C*

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

#### 848 *Chronic Hepatitis B*

849 Transient ALT elevations are common during hepatitis B therapy with PEGASYS.  
850 Twenty-five percent and 27% of patients experienced elevations of 5 to 10 x ULN and  
851 12% and 18% had elevations of >10 x ULN during treatment of HBeAg negative and  
852 HBeAg positive disease, respectively. Flares have been accompanied by elevations of  
853 total bilirubin and alkaline phosphatase and less commonly with prolongation of PT and  
854 reduced albumin levels. Eleven percent of patients had dose modifications due to ALT  
855 flares and <1% of patients were withdrawn from treatment (see **WARNINGS: Hepatic**  
856 **Failure and Hepatitis Exacerbations** and **DOSAGE AND ADMINISTRATION:**  
857 **Dose Modifications**).

858 ALT flares of 5 to 10 x ULN occurred in 13% and 16% of patients, while ALT flares of  
859 >10 x ULN occurred in 7% and 12% of patients in HBeAg negative and HBeAg positive  
860 disease, respectively, after discontinuation of PEGASYS therapy.

### 861 Thyroid Function

862 PEGASYS alone or in combination with COPEGUS was associated with the  
863 development of abnormalities in thyroid laboratory values, some with associated clinical  
864 manifestations. In the hepatitis C studies, hypothyroidism or hyperthyroidism requiring  
865 treatment, dose modification or discontinuation occurred in 4% and 1% of PEGASYS  
866 treated patients and 4% and 2% of PEGASYS and COPEGUS treated patients,  
867 respectively. Approximately half of the patients, who developed thyroid abnormalities  
868 during PEGASYS treatment, still had abnormalities during the follow-up period (see  
869 **PRECAUTIONS: Laboratory Tests**).

### 870 Immunogenicity

#### 871 *Chronic Hepatitis C*

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

#### 876 *Chronic Hepatitis B*

877 Twenty-nine percent (42/143) of hepatitis B patients treated with PEGASYS for 24  
878 weeks developed binding antibodies to interferon alfa-2a, as assessed by an ELISA assay.

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879 Thirteen percent of patients (19/143) receiving PEGASYS developed low-titer  
880 neutralizing antibodies (using an assay with a sensitivity of 100 INU/mL).

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

886 Additionally, the observed incidence of antibody positivity in these assays may be  
887 influenced by several factors including sample timing and handling, concomitant  
888 medications, and underlying disease. For these reasons, comparison of the incidence of  
889 antibodies to PEGASYS with the incidence of antibodies to other products may be  
890 misleading.

### 891 Postmarketing Experience

892 The following adverse reactions have been identified and reported during post-approval  
893 use of PEGASYS therapy: dehydration, hearing impairment, hearing loss, and serious  
894 skin reactions (see **WARNINGS: Hypersensitivity**). Additionally, pure red cell aplasia  
895 (PRCA) has been reported with PEGASYS alone or in combination with COPEGUS.  
896 Because these reactions are reported voluntarily from a population of uncertain size, it is  
897 not always possible to reliably estimate their frequency or establish a causal relationship  
898 to drug exposure. Decisions to include these reactions in labeling are typically based on  
899 one or more of the following factors: (1) seriousness of the reaction, (2) frequency of  
900 reporting or (3) strength of causal connection to PEGASYS.

### 901 OVERDOSAGE

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

### 908 DOSAGE AND ADMINISTRATION

909 There are no safety and efficacy data on treatment of chronic hepatitis C or hepatitis B for  
910 longer than 48 weeks. For patients with hepatitis C, consideration should be given to  
911 discontinuing therapy after 12 to 24 weeks of therapy if the patient has failed to  
912 demonstrate an early virologic response defined as undetectable HCV RNA or at least a  
913 2log<sub>10</sub> reduction from baseline in HCV RNA titer by 12 weeks of therapy (see  
914 **CLINICAL STUDIES**).

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

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920 PEGASYS should be inspected visually for particulate matter and discoloration before  
921 administration, and not used if particulate matter is visible or product is discolored. Vials  
922 and prefilled syringes with particulate matter or discoloration should be returned to the  
923 pharmacist.

### 924 **Chronic Hepatitis C**

#### 925 **PEGASYS Monotherapy**

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

#### 929 **PEGASYS and COPEGUS Combination Therapy**

930 The recommended dose of PEGASYS when used in combination with ribavirin for  
931 chronic hepatitis C is 180 µg (1.0 mL vial or 0.5 mL prefilled syringe) once weekly. The  
932 recommended dose of COPEGUS and duration for PEGASYS/COPEGUS therapy is  
933 based on viral genotype (see [Table 7](#)).

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

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

#### 939 **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

940 Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks (see [Table 3](#)).

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

942

### 943 **CHC with HIV Coinfection**

#### 944 **PEGASYS Monotherapy**

945 The recommended dose of PEGASYS monotherapy for chronic hepatitis C in patients  
946 coinfecting with HIV is 180 µg (1.0 mL vial or 0.5 mL prefilled syringe) once weekly for  
947 48 weeks by subcutaneous administration in the abdomen or thigh.

#### 948 **PEGASYS/COPEGUS Combination Therapy**

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

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

### 954 **Chronic Hepatitis B**

#### 955 **PEGASYS Monotherapy**

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

#### 959 **Dose Modifications**

960 **If severe adverse reactions or laboratory abnormalities develop during combination**  
961 **COPEGUS/PEGASYS therapy, the dose should be modified or discontinued, if**  
962 **appropriate, until the adverse reactions abate. If intolerance persists after dose**  
963 **adjustment, COPEGUS/PEGASYS therapy should be discontinued.**

### 964 **PEGASYS**

#### 965 **General**

966 When dose modification is required for moderate to severe adverse reactions (clinical  
967 and/or laboratory), initial dose reduction to 135 µg (which is 0.75 mL for the vials or  
968 adjustment to the corresponding graduation mark for the syringes) is generally adequate.  
969 However, in some cases, dose reduction to 90 µg (which is 0.5 mL for the vials or  
970 adjustment to the corresponding graduation mark for the syringes) may be needed.  
971 Following improvement of the adverse reaction, re-escalation of the dose may be  
972 considered (see **WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS**).

#### 973 **Hematological**

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

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

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975 Psychiatric: Depression

976 **Table 9 Guidelines for Modification or Discontinuation of PEGASYS**  
 977 **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 µg (in some cases dose reduction to 90 µg 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		

## 978 Renal Function

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

## 982 Liver Function

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

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

990 In chronic hepatitis B patients with elevations in ALT (>5 x ULN), more frequent  
 991 monitoring of liver function should be performed and consideration should be given to  
 992 either reducing the dose of PEGASYS to 135 µg or temporarily discontinuing treatment.

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993 After PEGASYS dose reduction or withholding, therapy can be resumed after ALT flares  
994 subside.

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

## 997 COPEGUS

### 998 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

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

1000

1001 Once COPEGUS has been withheld due to a laboratory abnormality or clinical  
1002 manifestation, an attempt may be made to restart COPEGUS at 600 mg daily and further  
1003 increase the dose to 800 mg daily depending upon the physician's judgment. However, it  
1004 is not recommended that COPEGUS be increased to the original dose (1000 mg or  
1005 1200 mg).

### 1006 Renal Impairment

1007 COPEGUS should not be used in patients with creatinine clearance <50 mL/min (see  
1008 [CLINICAL PHARMACOLOGY, WARNINGS](#) and [COPEGUS Package Insert](#)).

### 1009 HOW SUPPLIED

#### 1010 Single Dose Vial

1011 Each PEGASYS (peginterferon alfa-2a) 180 µg single use, clear glass vial provides  
1012 1.0 mL containing 180 µg peginterferon alfa-2a for sc injection. Each package contains 1  
1013 vial (NDC 0004-0350-09).

#### 1014 Prefilled Syringes Monthly Convenience Pack

1015 Four prefilled syringes of PEGASYS (peginterferon alfa-2a), 180 µg single use,  
1016 graduated, clear glass prefilled syringes, in a box with 4 needles and 4 alcohol swabs  
1017 (NDC 0004-0352-39). Each syringe is a 0.5 mL (½ cc) volume syringe supplied with a  
1018 27-gauge, ½-inch needle with needle-stick protection device.

### 1019 Storage

1020 Store in the refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect  
1021 from light. Vials and prefilled syringes are for single use only. Discard any unused  
1022 portion.

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1024 COPEGUS and PEGASYS are trademarks of Hoffmann-La Roche Inc.

1025 PI Revised: March 2010

1026

### MEDICATION GUIDE

1027

### PEGASYS®

1028

### (peginterferon alfa-2a)

1029 Before you start taking PEGASYS (PEG-ah-sis), alone or in combination with  
1030 COPEGUS® (Co-PEG-UHS), please read this Medication Guide carefully. Read this  
1031 Medication Guide each time you refill your prescription in case new information has  
1032 been added and make sure the pharmacist has given you the medicine your healthcare  
1033 provider prescribed for you. Reading the information in this Medication Guide does not  
1034 take the place of talking with your healthcare provider.

1035 If you are taking PEGASYS in combination with COPEGUS, you should also read the  
1036 Medication Guide for COPEGUS (ribavirin, USP) Tablets.

### 1037 **What is the most important information I should know about PEGASYS** 1038 **therapy?**

1039 PEGASYS, taken alone or in combination with COPEGUS, is a treatment for some  
1040 people who are infected with hepatitis C virus. PEGASYS taken alone is a treatment for  
1041 some people who are infected with the hepatitis B virus. However, PEGASYS and  
1042 COPEGUS can have serious side effects that may cause death in rare cases. Before  
1043 starting PEGASYS therapy, you should talk with your healthcare provider about the  
1044 possible benefits and the possible side effects of treatment, to decide if either of these  
1045 treatments is right for you. If you begin treatment you will need to see your healthcare  
1046 provider regularly for examinations and blood tests to make sure your treatment is  
1047 working and to check for side effects.

1048 The most serious possible side effects of PEGASYS taken alone or in combination with  
1049 COPEGUS include:

### 1050 **Problems with Pregnancy:**

1051 **Taking PEGASYS in combination with COPEGUS tablets can cause death, serious**  
1052 **birth defects or other harm to your unborn child. Therefore, if you are pregnant or**  
1053 **your partner is pregnant or plans to become pregnant, do not take**  
1054 **PEGASYS/COPEGUS combination therapy. Female patients and female partners**  
1055 **of male patients being treated with PEGASYS/COPEGUS combination therapy**  
1056 **must not become pregnant during treatment and for 6 months after treatment has**  
1057 **stopped. During this time, you must have pregnancy tests that show you are not**  
1058 **pregnant. You must also use two effective forms of birth control during therapy and**  
1059 **for 6 months after stopping therapy. Male patients should use a condom with**  
1060 **spermicide as one of the two forms.** You must use birth control even if you believe that  
1061 you are not fertile or that your fertility is low. You should talk to your healthcare provider  
1062 about birth control for you and your partner.

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1063 **If you are pregnant, you or your male partner must not take PEGASYS/COPEGUS**  
1064 **combination therapy. If you or your partner are being treated and you become**  
1065 **pregnant either during treatment or within 6 months of stopping treatment, call**  
1066 **your healthcare provider right away.**

1067 If you or a female sexual partner becomes pregnant, you should tell your healthcare  
1068 provider. There is a Ribavirin Pregnancy Registry that collects information about  
1069 pregnancy outcomes of female patients and female partners of male patients exposed to  
1070 ribavirin. You or your healthcare provider are encouraged to contact the Registry at 1-  
1071 800-593-2214.

### 1072 **Mental health problems and suicide:**

1073 PEGASYS and PEGASYS/COPEGUS combination therapy may cause some patients to  
1074 develop mood or behavioral problems. Signs of these problems include irritability  
1075 (getting easily upset), depression (feeling low, feeling bad about yourself or feeling  
1076 hopeless), and anxiety. Some patients may have aggressive behavior. Former drug addicts  
1077 may fall back into drug addiction or overdose. Some patients think about hurting or  
1078 killing themselves or other people and some have killed (suicide) or hurt themselves or  
1079 hurt other people. You must tell your healthcare provider if you are being treated for a  
1080 mental illness or have a history of mental illness, including depression and suicidal  
1081 behavior or if you are or have ever been addicted to drugs or alcohol. Call your  
1082 healthcare provider immediately if you develop any of these problems while on  
1083 PEGASYS treatment.

### 1084 **Heart problems:**

1085 Some patients taking PEGASYS or PEGASYS/COPEGUS therapies may develop  
1086 problems with their heart, including low blood pressure, fast heart rate, and very rarely,  
1087 heart attacks. Tell your healthcare provider if you have had any heart problems in the  
1088 past.

### 1089 **Blood problems:**

1090 Many patients taking PEGASYS have had a drop in the number of their white blood cells  
1091 and their platelets. If the numbers of these blood cells are too low, you could be at risk for  
1092 serious infections or bleeding.

1093 COPEGUS causes a decrease in the number of your red blood cells (anemia). This can be  
1094 dangerous, especially for patients who already have heart or circulatory (cardiovascular)  
1095 problems. If you have or have ever had any cardiovascular problems, talk with your  
1096 healthcare provider before taking the combination of PEGASYS and COPEGUS.

### 1097 **Liver problems:**

1098 Infrequently, some patients with hepatitis C and liver scarring can develop sudden severe  
1099 worsening (failure) of their liver disease while taking PEGASYS. Patients infected with  
1100 both the hepatitis C virus and HIV can have an increased chance of having liver failure  
1101 during PEGASYS treatment.

## PEGASYS® (peginterferon alfa-2a)

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1102 Some patients taking PEGASYS for hepatitis B have had a rise in a blood test that  
1103 measures liver inflammation. If you have a rise in this blood test, your liver may need to  
1104 be watched more closely with additional blood tests.

### 1105 **Infections:**

1106 Some patients taking interferon have had serious infections. Sometimes these infections  
1107 have been fatal. If you develop a fever that does not go away or gets higher, call your  
1108 healthcare provider right away. Your healthcare provider will need to examine you to rule  
1109 out your having a serious infection.

### 1110 **Eye problems:**

1111 Changes in vision such as a decrease or loss of vision (blindness) may happen in some  
1112 patients. You should have an eye exam before you take PEGASYS. If you have eye  
1113 problems or have had them in the past you may need eye exams while you are taking  
1114 PEGASYS. Tell your healthcare provider or eye doctor right away if you have changes in  
1115 your vision while taking PEGASYS.

### 1116 **Body organ problems:**

1117 PEGASYS may cause lung problems including: trouble breathing, pneumonia,  
1118 inflammation of lung tissue, and new or worse high blood pressure in the lungs  
1119 (pulmonary hypertension), which can be severe and may in some cases lead to death.  
1120 Certain symptoms like severe stomach pain may mean that your internal organs are being  
1121 damaged. Cases of weakness, loss of coordination and numbness due to stroke have been  
1122 reported in patients taking PEGASYS/COPEGUS, including patients with few or no  
1123 reported risk factors for stroke.

### 1124 **Call your healthcare provider immediately if you develop any of these** 1125 **conditions:**

- 1126 • **You become very depressed, think about suicide or injuring/killing another**  
1127 **person**
- 1128 • **You have severe chest pain**
- 1129 • **You have trouble breathing**
- 1130 • **You have a change in your vision**
- 1131 • **You become pregnant**
- 1132 • **You notice unusual bleeding or bruising**
- 1133 • **You have psoriasis (a skin disease) and it gets worse while taking PEGASYS**
- 1134 • **You have weakness, loss of coordination, numbness or difficulty speaking**
- 1135 • **High fever or a fever that does not go away**
- 1136 • **You have severe stomach pain or lower back pain**
- 1137 • **Bloody diarrhea**
- 1138 • **Skin rash can occur in patients taking PEGASYS. In some patients a rash**  
1139 **can be serious. If you develop a rash with fever, blisters, or sores in your**  
1140 **mouth, nose or eyes or conjunctivitis (red or inflamed eyes, like “pink eye”),**  
1141 **stop using PEGASYS and call your doctor right away**

1142

## PEGASYS® (peginterferon alfa-2a)

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1143 *For more information on possible side effects with PEGASYS therapy, alone or in*  
1144 *combination with COPEGUS, please read the section on “[What are the possible side](#)*  
1145 *[effects of PEGASYS, and PEGASYS taken with COPEGUS?](#)” in this Medication*  
1146 *Guide. You should also read the Medication Guide for COPEGUS tablets if you are*  
1147 *taking that medicine with PEGASYS.*

### 1148 **What is PEGASYS?**

1149 PEGASYS is a drug used to treat adults who have a lasting (chronic) infection with  
1150 hepatitis C virus or hepatitis B virus and who show signs that the virus is damaging the  
1151 liver. Patients with hepatitis have the virus in their blood and in their liver. PEGASYS  
1152 reduces the amount of hepatitis C virus in the body and helps the body’s immune system  
1153 fight the virus. The drug COPEGUS are tablets that may be taken with PEGASYS to help  
1154 fight the virus infection. Do not take COPEGUS by itself.

1155 In some patients that have received PEGASYS treatment for approximately one year to  
1156 treat hepatitis C, the amount of the hepatitis virus in the body was decreased to a level so  
1157 low that it could not be measured by blood tests. After 3 months of therapy, your  
1158 healthcare provider may ask you to have a blood test to help determine how you are  
1159 responding to your treatment.

1160 It is not known if PEGASYS, used alone or in combination with COPEGUS, can cure  
1161 hepatitis (permanently eliminate the virus) or if it can prevent liver failure or liver cancer  
1162 that is caused by hepatitis infection.

1163 It is also not known if PEGASYS, alone or in combination with COPEGUS, will prevent  
1164 one infected person from infecting another person with hepatitis.

### 1165 **Who should not take PEGASYS, or PEGASYS with COPEGUS?**

1166 Do not take PEGASYS or PEGASYS/COPEGUS therapy if you:

- 1167 • are pregnant, planning to get pregnant during treatment or during the 6 months after  
1168 treatment or breast-feeding
- 1169 • are a male patient with a female sexual partner who is pregnant or plans to become  
1170 pregnant at any time while you are being treated with COPEGUS or during the 6  
1171 months after your treatment has ended
- 1172 • have hepatitis caused by your immune system attacking your liver (autoimmune  
1173 hepatitis)
- 1174 • have unstable or severe liver disease
- 1175 • had an allergic reaction to another alpha interferon or are allergic to any of the  
1176 ingredients in PEGASYS or COPEGUS tablets
- 1177 • Do not take PEGASYS, alone or in combination with COPEGUS, if you have  
1178 abnormal red blood cells such as sickle-cell anemia or thalassemia major.  
1179

### 1180 **If you have ever had any of the following conditions or serious medical** 1181 **problems, tell your healthcare provider before you start taking PEGASYS:**

- 1182 • History of or current severe mental illness (such as depression or anxiety)
- 1183 • History of drug or alcohol addiction or abuse

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- 1184 • History of heart disease or previous heart attack
- 1185 • History of cancer
- 1186 • Autoimmune disease (where the body's immune system attacks the body's own
- 1187 cells), such as psoriasis (a skin disease), systemic lupus erythematosus, rheumatoid
- 1188 arthritis
- 1189 • Kidney problems
- 1190 • Blood disorders (bleeding problems)
- 1191 • Diabetes (high blood sugar)
- 1192 • Problems with the thyroid gland
- 1193 • Liver problems, other than hepatitis C or hepatitis B
- 1194 • Colitis (an inflammation of the bowels)
- 1195 • Eye problems
- 1196 • Sleep problems
- 1197 • HIV infection
- 1198 • Organ transplant and are taking medicine that keeps your body from rejecting your
- 1199 transplant (suppresses your immune system)

1200

1201 **Tell your healthcare provider about all the medicines you take**, including prescription  
1202 and non-prescription medicines, vitamins and herbal supplements. PEGASYS and certain  
1203 other medicines may affect each other causing side effects.

1204 Especially tell your healthcare provider if you take:

- 1205 • the anti-hepatitis B medicine telbivudine (Tyzeka). See **“What are the possible side**  
1206 **effects of PEGASYS, and PEGASYS taken with COPEGUS”**.
- 1207 • Theophylline: Your healthcare provider may need to monitor the amount of  
1208 theophylline in your body and make changes to your theophylline dose.
- 1209 • HIV medications called nucleoside reverse transcriptase inhibitors (abacavir,  
1210 didanosine, emtricitabine, lamivudine, tenofovir, stavudine or zidovudine). Some  
1211 patients developed serious liver problems including death.
- 1212 • Didanosine: Do not take COPEGUS and didanosine.

1213

1214 If you have any questions about your health condition or about taking PEGASYS alone  
1215 or in combination with COPEGUS, you should talk to your healthcare provider.

### 1216 **How should I take PEGASYS, or PEGASYS with COPEGUS?**

1217 PEGASYS is given by injection under the skin (subcutaneous injection). PEGASYS  
1218 comes in two different forms (a liquid in a single use vial and a liquid in a prefilled  
1219 syringe). Your healthcare provider will determine which is best for you. Your healthcare  
1220 provider will also decide whether you will take PEGASYS alone or with COPEGUS.  
1221 Your dose of PEGASYS is given as a single injection once per week. At some point, your  
1222 healthcare provider may change your dose of PEGASYS or COPEGUS. Do not change  
1223 your dose unless your healthcare provider tells you to change it. It is important that you  
1224 take PEGASYS and COPEGUS exactly as your healthcare provider tells you. Once you  
1225 start treatment with PEGASYS, do not switch to another brand of interferon without

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1226 talking to your healthcare provider. Other interferons may not have the same effect on the  
1227 treatment of your disease. Switching brands will also require a change in your dose.

1228 Take your prescribed dose of PEGASYS once a week, on the same day of each week and  
1229 at approximately the same time. Your total dose of COPEGUS tablets should be divided  
1230 so you take it twice a day with food (breakfast and dinner). Taking half your dose of  
1231 COPEGUS in the morning and the other half at night will keep the medicine in your body  
1232 at a steady level. Do not take more than your prescribed dose of PEGASYS or  
1233 COPEGUS. **Be sure to read the Medication Guide for COPEGUS (ribavirin, USP)**  
1234 **for complete instructions on how to take the COPEGUS tablets.**

1235 Your healthcare provider will train you and/or the person that will be giving you the  
1236 PEGASYS injections on the proper way to give injections. Whether you give yourself the  
1237 injection or another person gives the injection to you, it is important that you are  
1238 comfortable with preparing and injecting a dose of PEGASYS, and you understand the  
1239 instructions in “[How do I inject PEGASYS?](#)” **At the end of this guide there are**  
1240 **detailed instructions on how to prepare and give yourself an injection of PEGASYS**  
1241 **using the form your healthcare provider has prescribed for you.**

1242 If you miss a dose and you remember **within 2 days** of when you should have taken  
1243 PEGASYS, give yourself an injection of PEGASYS as soon as you remember. Take your  
1244 next dose on the day you would usually take it. If **more than 2 days** have passed, ask  
1245 your healthcare provider what you should do. If you miss a dose of COPEGUS, take the  
1246 missed dose as soon as you remember during the same day. Do not take 2 doses too close  
1247 together in time. If it is late in the day, wait until the next day and go back on schedule.  
1248 **Do not double the next dose.**

1249 If you take more than the prescribed amount of PEGASYS, call your healthcare provider  
1250 right away. Your healthcare provider may want to examine you and take blood for  
1251 testing.

1252 You must get regular blood tests to help your healthcare provider check how the  
1253 treatment is working and to check for side effects.

### 1254 **What should I avoid while taking PEGASYS, or PEGASYS with COPEGUS?**

- 1255 • If you are pregnant do not start taking or continue taking COPEGUS in combination  
1256 with PEGASYS. (See “[What is the most important information I should know](#)  
1257 [about PEGASYS therapy? Problems with Pregnancy](#)”.)
- 1258 • Avoid becoming pregnant while taking PEGASYS, alone or in combination with  
1259 COPEGUS. PEGASYS, alone or in combination with COPEGUS, may harm your  
1260 unborn child (death or serious birth defects) or cause you to lose your baby  
1261 (miscarry). (See “[What is the most important information I should know about](#)  
1262 [PEGASYS therapy? Problems with Pregnancy](#)”.)
- 1263 • Do not breast-feed your baby while on PEGASYS, alone or in combination with  
1264 COPEGUS.
- 1265 • **Drinking alcohol**, including beer, wine and liquor. This may make your liver disease  
1266 worse.

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- 1267 • **Taking other medicines.** Take only medicines prescribed or approved by your  
1268 healthcare provider. These include prescription and nonprescription medicines and  
1269 herbal supplements.

### 1270 **What are the possible side effects of PEGASYS, and PEGASYS taken with** 1271 **COPEGUS?**

1272 *Also see “What is the most important information I should know about PEGASYS*  
1273 *therapy?” in this Medication Guide.*

1274 PEGASYS and PEGASYS/COPEGUS combination therapy can cause serious side  
1275 effects including:

- 1276 • See “*What is the most important information I should know about PEGASYS*  
1277 *therapy?”*.
- 1278 • **Blood problems including anemia:** Anemia is a reduction in the number of red  
1279 blood cells you have, which can be dangerous, especially if you have heart or  
1280 breathing problems. Tell your healthcare provider right away if you feel tired, have  
1281 chest pain or shortness of breath. These may be signs of low red blood cell counts.
- 1282 • **Serious infections.**
- 1283 • **Stroke:** Some patients may experience weakness, loss of coordination, and numbness  
1284 due to stroke.
- 1285 • **Autoimmune problems:** Some patients may develop a disease where the body’s own  
1286 immune system begins to attack itself (autoimmune disease) while on PEGASYS  
1287 therapy. These diseases can include rheumatoid arthritis, systemic lupus  
1288 erythematosus, psoriasis or thyroid problems. In some patients who already have an  
1289 autoimmune disease, the disease may worsen while on PEGASYS therapy.
- 1290 • **Heart problems:** PEGASYS may cause some patients to experience chest pain, and  
1291 very rarely a heart attack. Patients who already have heart disease could be at greatest  
1292 risk. Tell your healthcare provider if you have or have had a heart problem in the past.
- 1293 • **Liver problems:** Some patients may develop worsening of liver function. Some of  
1294 the symptoms may include stomach bloating, confusion, brown urine, and yellow  
1295 eyes. Tell your healthcare provider immediately if any of these symptoms occur.
- 1296 • **Nerve problems:** People who take PEGASYS or other alpha interferon products with  
1297 telbivudine (Tyzeka) can have nerve problems such as continuing numbness, tingling,  
1298 or burning sensation in the arms or legs (peripheral neuropathy). Call your healthcare  
1299 provider if you have any of these symptoms.
- 1300 • **Harm to unborn children:** PEGASYS and PEGASYS/COPEGUS may cause birth  
1301 defects or death of an unborn child. For more details, see “*What is the most important*  
1302 *information I should know about PEGASYS therapy?” in this Medication Guide.*  
1303

1304 Common, but less serious, side effects include:

- 1305 • **Flu-like symptoms:** Most patients who take PEGASYS have flu-like symptoms that  
1306 usually lessen after the first few weeks of treatment. Flu-like symptoms may include  
1307 fever, chills, muscle aches, joint pain, and headaches. Taking pain and fever reducers  
1308 such as acetaminophen or ibuprofen before you take PEGASYS can help with these

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- 1309 symptoms. You can also try taking PEGASYS at night. You may be able to sleep  
1310 through the symptoms.
- 1311 • **Extreme fatigue (tiredness):** Many patients may become extremely tired while on  
1312 PEGASYS therapy.
  - 1313 • **Upset stomach:** Nausea, taste changes, diarrhea, and loss of appetite occur  
1314 commonly.
  - 1315 • **Blood sugar problems:** Some patients may develop a problem with the way their  
1316 body controls their blood sugar and may develop diabetes.
  - 1317 • **Thyroid problems:** Some patients develop changes in the function of their thyroid.  
1318 Symptoms of thyroid changes include the inability to concentrate, feeling cold or hot  
1319 all the time, a change in your weight, and changes to your skin.
  - 1320 • **Skin reactions:** Some patients may develop redness, swelling, dry or itchy skin at the  
1321 site of injection. If after several days these symptoms do not disappear, contact your  
1322 healthcare provider. You may get a rash during therapy. If this occurs, your  
1323 healthcare provider may recommend medicine to treat the rash.
  - 1324 • **Hair thinning:** Temporary hair loss is not uncommon during treatment with  
1325 PEGASYS.
  - 1326 • **Trouble sleeping**

1327 These are not all of the side effects of PEGASYS, and PEGASYS taken with COPEGUS.  
1328 Your healthcare provider or pharmacist can give you a more complete list. Call your  
1329 doctor for medical advice about side effects. You may report side effects to FDA at 1-  
1330 800-FDA-1088. You may also report side effects to Genentech at 1-888-835-2555.

1331 Talk to your healthcare provider if you are worried about side effects or find them very  
1332 bothersome.

### 1333 **General advice about prescription medicines**

1334 Medicines are sometimes prescribed for purposes other than those listed in a Medication  
1335 Guide. If you have any concerns or questions about PEGASYS, contact your healthcare  
1336 provider. Do not use PEGASYS for a condition or person other than that for which it is  
1337 prescribed. If you want to know more about PEGASYS, your healthcare provider or  
1338 pharmacist will be able to provide you with detailed information that is written for  
1339 healthcare providers.

1340 If you are taking COPEGUS (ribavirin, USP) in combination with PEGASYS, also read  
1341 the Medication Guide supplied with that medicine.

1342 Keep this and all drugs out of the reach of children.

1343 This Medication Guide has been approved by the US Food and Drug Administration.

1344 MG Revised: March 2010

## PEGASYS® (peginterferon alfa-2a)

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### 1345 Medication Guide Appendix: Instructions for Preparing and Giving a Dose with a 1346 PEGASYS® Prefilled Syringe

#### 1347 **How should I store PEGASYS Prefilled Syringes?**

1348 PEGASYS must be stored in the refrigerator at a temperature of 2°C to 8°C (36°F to  
1349 46°F). Do not leave PEGASYS outside of the refrigerator for more than 24 hours. Do not  
1350 freeze PEGASYS. Keeping PEGASYS at temperatures outside the recommended range  
1351 can destroy the medicine.

1352 Each PEGASYS prefilled syringe can only be used once. Discard after use.

1353 To avoid product foaming, do not shake the prefilled syringe of PEGASYS.

1354 Protect PEGASYS from light during storage.

1355 Keep this and all other medicines out of the reach of children.

#### 1356 **How do I prepare and inject PEGASYS?**

1357 You should read through all of these directions and ask your healthcare provider for help  
1358 if you have any questions before trying to give yourself an injection. It is important to  
1359 follow these directions carefully. Talk to your healthcare provider if you have any  
1360 questions about PEGASYS.

1361 Your healthcare provider may not want you to take all the medicine that comes in the  
1362 prefilled syringe. To appropriately administer the dose that your healthcare provider tells  
1363 you to take, you may have to get rid of some of the medicine before injecting the  
1364 medicine.

1365 If you ever switch between using prefilled syringes and vials, talk to your healthcare  
1366 provider about how much PEGASYS to use. Equal volumes of liquid from the prefilled  
1367 syringes and the vials DO NOT contain the same amount of PEGASYS. If you switch  
1368 between prefilled syringes and vials, you will have to adjust the volume of liquid that you  
1369 use to give your injection. If you do not adjust this, you could accidentally take too much  
1370 or too little of your medicine.

1371 If you are giving this injection to someone else, a healthcare provider must teach you how  
1372 to avoid needle sticks. Being stuck by a used needle can pass diseases on to you.

1373 The prefilled syringes are used for injecting PEGASYS under the surface of the skin  
1374 (subcutaneous).

1375

1376

1377 1. Collect all the materials you will need before you start to give the injection:

- 1378 • One PEGASYS prefilled syringe Monthly Convenience Pack containing an  
1379 inner carton holding the PEGASYS prefilled syringe
- 1380 • A puncture-resistant container for cleaning up when you are finished

1381

1382 2. Open the convenience pack and look at the contents.

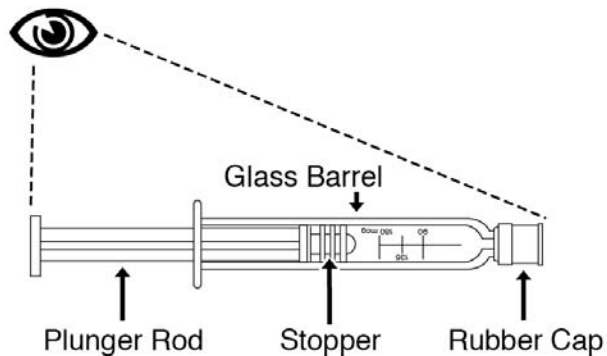
- 1383 • Each convenience pack has everything you need for the PEGASYS injection.

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- 1384 – 4 single use syringes filled with medicine (should be colorless to light  
1385 yellow)
- 1386 – four 27-gauge, ½-inch needles with needle-stick protection device
- 1387 – 4 alcohol swabs
- 1388 3. Take the syringe out of the refrigerator. If there is foam in the solution, put it back in  
1389 the refrigerator for use at a later time and use another syringe.
- 1390 4. Lay the syringe on a flat clean surface and wait a few minutes until it reaches room  
1391 temperature. If you notice condensation water on the outside of the syringe, wait  
1392 another few minutes until it disappears.
- 1393 5. Wash your hands with soap and warm water to prevent infection.
- 1394 6. After the syringe has warmed up, pick it up by the glass barrel and look at it carefully.
- 1395 • Do not use PEGASYS if:  
1396 – the medicine is cloudy  
1397 – the medicine has particles floating in it  
1398 – the medicine is any color besides colorless to light yellow  
1399 – the expiration date has passed

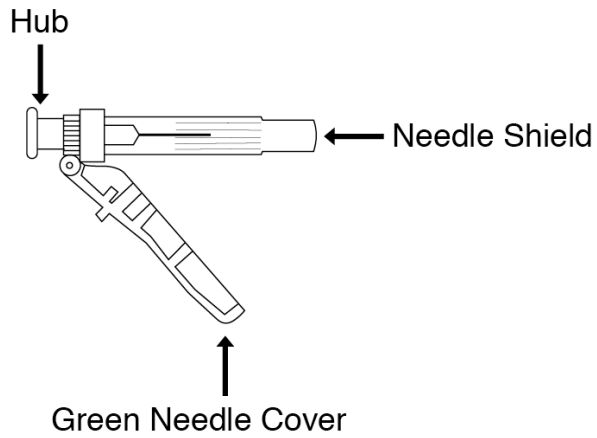


- 1400
- 1401 7. Attachment of the needle to the PEGASYS prefilled syringe:  
1402 • Remove the needle from its package. Do not remove the needle shield yet.  
1403 Keep the needle covered until just before you give the injection.

# PEGASYS® (peginterferon alfa-2a)

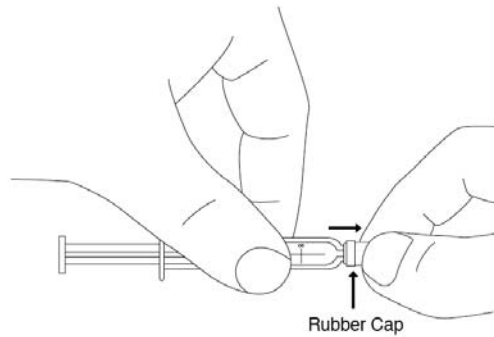
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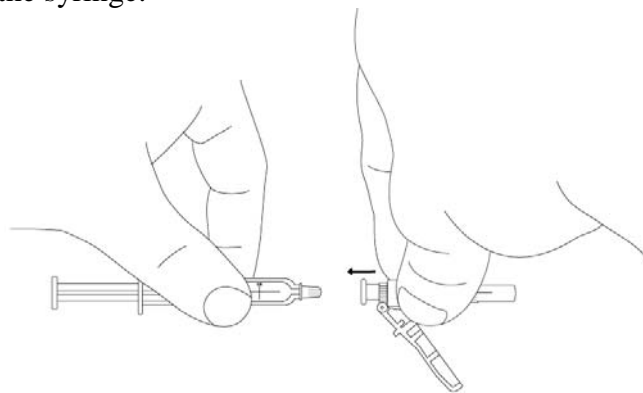
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- Remove and discard the rubber cap from the tip of the syringe barrel.



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1410

- Hold the needle close to the hub where the green needle cover connects.
- Put the needle onto the syringe by using an easy twisting motion to tighten the needle onto the syringe.



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## PEGASYS® (peginterferon alfa-2a)

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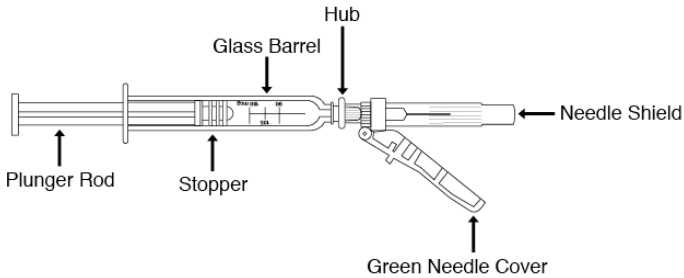
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- Here is a picture of the assembled syringe:



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

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### 8. Decide where you will give the injection.

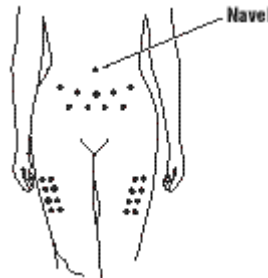
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- Pick a place on your stomach or thigh (see the picture below). Avoid your navel and waistline. You should use a different place each time you give yourself an injection.



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### 9. 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.

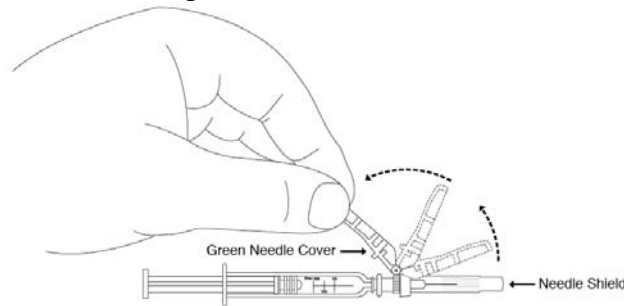
## PEGASYS® (peginterferon alfa-2a)

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1430 10. Prepare the syringe for injection.

- 1431
- 1432 • Pull the green needle cover back from the needle toward the syringe barrel.
  - 1433 The green needle cover will remain in the position you set, do not remove it.

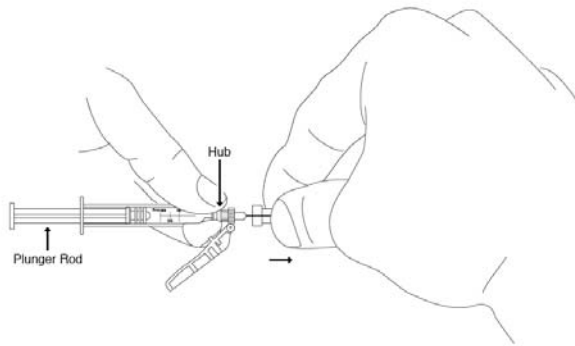


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- 1436
- Hold the syringe-needle assembly tightly at the hub.

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1442 11. Remove air bubbles from the syringe.

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12. Dose adjustment.

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- 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.

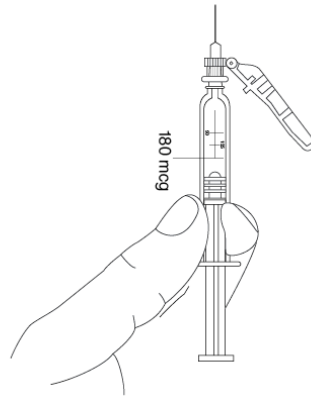
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- The syringe has markings for 180 mcg, 135 mcg, and 90 mcg. Your healthcare provider will tell you which mark to use.

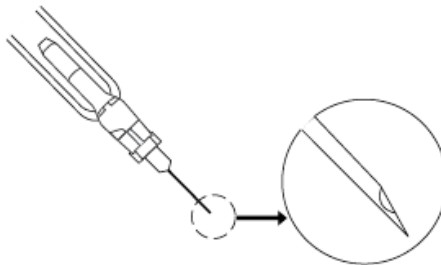


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- Once you know which mark to use, slowly and carefully press on the plunger rod of the syringe to push out medicine from the syringe. Keep pressing until the edge of the plunger stopper reaches the right mark on the side of the syringe.
- Do not decrease or increase your dose of PEGASYS unless your healthcare provider tells you to.

### 13. Give the injection of PEGASYS.

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



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



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- Hold the syringe like a pencil at a 45° to 90° angle to your skin. In one quick motion, insert the needle as far as it will go into the pinched area of skin. Pull the plunger of the syringe back very slightly. If blood comes into the syringe, the needle has entered a blood vessel. **Do not inject. Withdraw the needle and discard the syringe as outlined in step 14. Repeat the above steps with a new prefilled syringe and prepare a new site.**

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



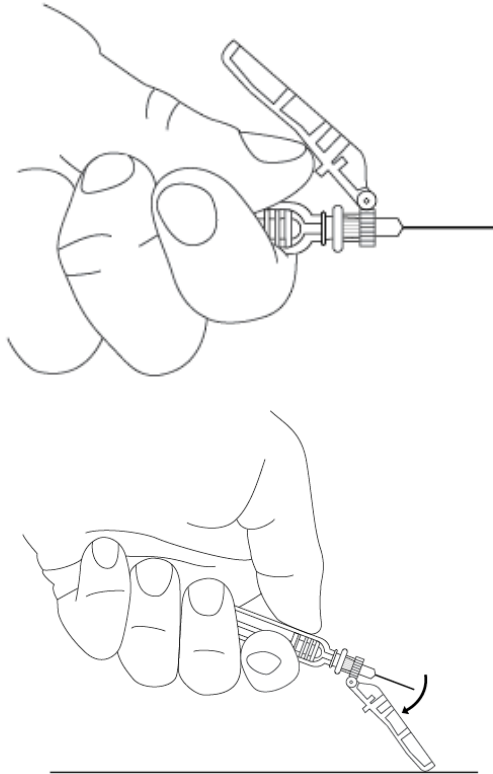
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- Pull out the needle at same angle you put it in.
- Wipe the area with an alcohol swab.

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



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

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

1499

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

1500

- The needles and syringes should never be reused.

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- 1501 • Place all used needles and syringes in a puncture-proof disposable container that is  
1502 available through your pharmacy or healthcare provider (Sharp's container).  
1503 • DO NOT use glass or clear plastic containers for disposal of needles and syringes.  
1504 • Dispose of the full container as instructed by your healthcare provider or pharmacist.  
1505

1506 **DO NOT throw the container in your household trash. DO NOT recycle. Keep the**  
1507 **container out of the reach of children.**

1508 MG Appendix: Prefilled Syringe revision date: April 2009

### 1509 **Medication Guide Appendix: Instructions for Preparing and Giving a Dose with a** 1510 **PEGASYS® Vial**

#### 1511 **How should I store PEGASYS vials?**

1512 PEGASYS must be stored in the refrigerator at a temperature of 2°C to 8°C (36°F to  
1513 46°F). Do not leave PEGASYS outside of the refrigerator for more than 24 hours. Do not  
1514 freeze PEGASYS. Keeping PEGASYS at temperatures outside the recommended range  
1515 can destroy the medicine.

1516 Each PEGASYS vial can only be used once. Discard after use.

1517 Do not shake the vial of PEGASYS. If PEGASYS is shaken too hard, it will not work  
1518 properly.

1519 Protect PEGASYS from light during storage.

1520 Keep this and all other medicines out of the reach of children.

#### 1521 **How do I inject PEGASYS?**

1522 The following instructions will help you learn how to measure your dose and give  
1523 yourself an injection of PEGASYS. You should read through all of these directions and  
1524 ask your healthcare provider for help if you have any questions before trying to give  
1525 yourself an injection. It is important to follow these directions carefully. Talk to your  
1526 healthcare provider if you have any questions about PEGASYS.

1527 If you are giving an injection to someone else, a healthcare provider must teach you how  
1528 to avoid needle sticks. Being stuck by a used needle can pass diseases on to you.

- 1529 1. Collect all the materials you will need before you start to give the injection:  
1530 • One vial of PEGASYS  
1531 • One syringe and needle  
1532 • Several alcohol pads  
1533 • A puncture-resistant container to dispose of the needle and syringe when you are  
1534 finished  
1535 2. Check the date on the carton the PEGASYS comes in and make sure the expiration  
1536 date has not passed, then remove a vial from the package and look at the medicine.  
1537 • Do not use PEGASYS if:  
1538 – the medicine is cloudy  
1539 – the medicine has particles floating in it

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- 1540 – the medicine is any color besides colorless to light yellow
- 1541 – the expiration date has passed
- 1542 3. Warm the refrigerated medicine by gently rolling it in the palms of your hands for
- 1543 about one minute. Do not shake.
- 1544 4. Wash your hands with soap and warm water to prevent infection.
- 1545 5. Take the vial of PEGASYS and flip off the plastic top covering the vial opening, and
- 1546 clean the rubber stopper on the top of the vial with a different alcohol pad.

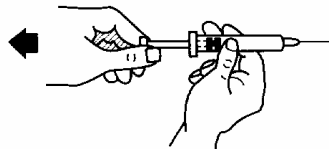


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1548 **If you are not sure how much medicine to use or which mark to use, STOP and call**

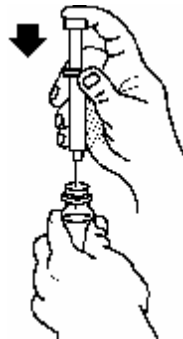
1549 **your healthcare provider right away.**

- 1550 6. Remove the needle and syringe from their packaging and attach the needle to the end
- 1551 of the syringe.
- 1552 • Pull the plunger back so the end of it is to the mark on the syringe barrel that
- 1553 matches the dose prescribed for you by your healthcare provider. This will pull air
- 1554 into the syringe barrel.



1555

- 1556 • Push the needle through the center of the stopper on the vial.
- 1557 • Slowly inject all the air from the syringe into the air space above the solution. Do
- 1558 not inject air into the fluid.



1559

- 1560 • Keep the needle inside the vial and turn both upside down. Hold the vial and
- 1561 syringe straight up. Slowly pull back on the plunger until the medicine is in the
- 1562 syringe up to the mark that matches your dose. Make sure the needle tip always
- 1563 stays in the medicine (not in the air space above it).

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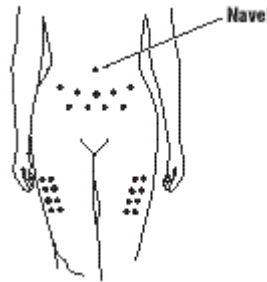
- 1565 • When the medicine is up to the right mark on the syringe barrel, take the syringe  
1566 and needle out of the rubber stopper on the vial.
- 1567 • Keep the syringe pointing up until you are ready to use it.
- 1568 • If you need to set the syringe down, make sure that you never let the needle touch  
1569 any surface.

1570 7. Remove air bubbles from the syringe.

- 1571 • Hold the syringe with the needle pointing up to the ceiling.
- 1572 • Using your thumb and finger, tap the syringe to bring air bubbles to the top.
- 1573 • Press the plunger in slightly to push air bubbles out of the syringe.

1574 8. Decide where you will give the injection.

- 1575 • Pick a place on your stomach or thigh (see the picture below). Avoid your navel  
1576 and waistline. You should use a different place each time you give yourself an  
1577 injection.



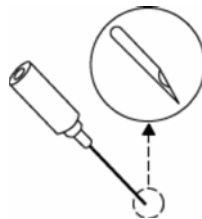
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1579 9. Prepare your skin for the injection.

- 1580 • To minimize the discomfort from injections, you may want to gently tap the area  
1581 where you plan to give yourself an injection.
- 1582 • Clean the area using an alcohol pad. Let the skin dry for 10 seconds.  
1583

1584 10. Give the injection of PEGASYS.

- 1585 • Position the point of the needle (the bevel) so it is facing up.  
1586



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- 1588 • Pinch a fold of skin on your stomach or thigh firmly between your thumb and  
1589 forefinger.

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



1601

- 1602
- Pull out the needle at same angle you put it in. Wipe the area with an alcohol pad.
- 1603
- 1604
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- 1607
11. For safety reasons, always place used syringes and needles in a puncture-resistant container immediately after use and never reuse them.
- If you are using a syringe with a needle-stick protection device, before you dispose of the syringe and needle, place the free end of the green cap on a flat surface and push down on it until it clicks and covers over the needle.

### 1608 **How should I dispose of materials used to inject PEGASYS?**

1609 There may be special state and local laws for disposal of used needles and syringes. Your  
1610 healthcare provider or pharmacist should provide you with instructions on how to  
1611 properly dispose of your used syringes and needles. Always follow these instructions.

1612 The instructions below should be used as a general guide for proper disposal:

- 1613
- 1614
- 1615
- 1616
- 1617
- 1618
- The needles and syringes should never be reused.
  - Place all used needles and syringes in a puncture-proof disposable container that is available through your pharmacy or healthcare provider (Sharp's container).
  - DO NOT use glass or clear plastic containers for disposal of needles and syringes.
  - Dispose of the full container as instructed by your healthcare provider or pharmacist.

1619 **DO NOT throw the container in your household trash. DO NOT recycle. Keep the**  
1620 **container out of the reach of children.**

**PEGASYS® (peginterferon alfa-2a)**

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1621 MG Appendix: Vial revision date: October 2008

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1624 **Hoffmann-La Roche Inc.**

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