

**COPEGUS®****(ribavirin, USP)****TABLETS****R<sub>x</sub> only**

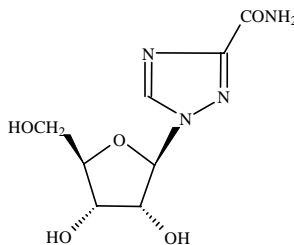
COPEGUS (ribavirin) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication (see WARNINGS).

The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin (see WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Information for Patients, and Pregnancy: Category X).

**DESCRIPTION**

COPEGUS, ribavirin, is a nucleoside analogue with antiviral activity. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and has the following structural formula:



The empirical formula of ribavirin is C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> and the molecular weight is 244.2. Ribavirin is a white to off-white powder. It is freely soluble in water and slightly soluble in anhydrous alcohol.

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33 COPEGUS (ribavirin) is available as a light pink to pink colored, flat, oval-shaped, film-  
34 coated tablet for oral administration. Each tablet contains 200 mg of ribavirin and the  
35 following inactive ingredients: pregelatinized starch, microcrystalline cellulose, sodium  
36 starch glycolate, cornstarch, and magnesium stearate. The coating of the tablet contains  
37 Chromatone-P® or Opadry® Pink (made by using hydroxypropyl methyl cellulose, talc,  
38 titanium dioxide, synthetic yellow iron oxide, and synthetic red iron oxide), ethyl  
39 cellulose (ECD-30), and triacetin.

### 40 Mechanism of Action

41 Ribavirin is a synthetic nucleoside analogue. The mechanism by which the combination  
42 of ribavirin and an interferon product exerts its effects against the hepatitis C virus has  
43 not been fully established.

### 44 CLINICAL PHARMACOLOGY

#### 45 Pharmacokinetics

46 Multiple dose ribavirin pharmacokinetic data are available for HCV patients who  
47 received ribavirin in combination with peginterferon alfa-2a. Following administration of  
48 1200 mg/day with food for 12 weeks mean±SD (n=39; body weight >75 kg) AUC<sub>0-12hr</sub>  
49 was 25,361±7110 ng·hr/mL and C<sub>max</sub> was 2748±818 ng/mL. The average time to reach  
50 C<sub>max</sub> was 2 hours. Trough ribavirin plasma concentrations following 12 weeks of dosing  
51 with food were 1662±545 ng/mL in HCV infected patients who received 800 mg/day  
52 (n=89), and 2112±810 ng/mL in patients who received 1200 mg/day (n=75; body weight  
53 >75 kg).

54 The terminal half-life of ribavirin following administration of a single oral dose of  
55 COPEGUS is about 120 to 170 hours. The total apparent clearance following  
56 administration of a single oral dose of COPEGUS is about 26 L/h. There is extensive  
57 accumulation of ribavirin after multiple dosing (twice daily) such that the C<sub>max</sub> at steady  
58 state was four-fold higher than that of a single dose.

#### 59 Effect of Food on Absorption of Ribavirin

60 Bioavailability of a single oral dose of ribavirin was increased by co-administration with  
61 a high-fat meal. The absorption was slowed (T<sub>max</sub> was doubled) and the AUC<sub>0-192h</sub> and  
62 C<sub>max</sub> increased by 42% and 66%, respectively, when COPEGUS was taken with a high-  
63 fat meal compared with fasting conditions (see **PRECAUTIONS** and **DOSAGE AND**  
64 **ADMINISTRATION**).

#### 65 Elimination and Metabolism

66 The contribution of renal and hepatic pathways to ribavirin elimination after  
67 administration of COPEGUS is not known. In vitro studies indicate that ribavirin is not a  
68 substrate of CYP450 enzymes.

**69 Special Populations****70 Race**

71 A pharmacokinetic study in 42 subjects demonstrated there is no clinically significant  
72 difference in ribavirin pharmacokinetics among Black (n=14), Hispanic (n=13) and  
73 Caucasian (n=15) subjects.

**74 Renal Dysfunction**

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

**80 Hepatic Impairment**

81 The effect of hepatic impairment on the pharmacokinetics of ribavirin following  
82 administration of COPEGUS has not been evaluated. The clinical trials of COPEGUS  
83 were restricted to patients with Child-Pugh class A disease.

**84 Pediatric Patients**

85 Pharmacokinetic evaluations in pediatric patients have not been performed.

**86 Elderly Patients**

87 Pharmacokinetic evaluations in elderly patients have not been performed.

**88 Gender**

89 Ribavirin pharmacokinetics, when corrected for weight, are similar in male and female  
90 patients.

**91 Drug Interactions**

92 In vitro studies indicate that ribavirin does not inhibit CYP450 enzymes.

**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, which could cause or  
103 worsen clinical toxicities (see **PRECAUTIONS: 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.

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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 CLINICAL STUDIES

#### 111 HCV Patients

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

118 In Study NV15801 (described as Study 4 in the PEGASYS Package Insert), patients were  
119 randomized to receive either PEGASYS 180 µg sc once weekly (qw) with an oral  
120 placebo, PEGASYS 180 µg qw with COPEGUS 1000 mg po (body weight <75 kg) or  
121 1200 mg po (body weight ≥75 kg) or Rebetron™ (interferon alfa-2b 3 MIU sc tiw plus  
122 ribavirin 1000 mg or 1200 mg po). All patients received 48 weeks of therapy followed by  
123 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment assignment was  
124 blinded. Sustained virological response was defined as undetectable (<50 IU/mL) HCV  
125 RNA on or after study week 68. PEGASYS in combination with COPEGUS resulted in a  
126 higher SVR compared to PEGASYS alone or interferon alfa-2b and ribavirin (**Table 1**).  
127 In all treatment arms, patients with viral genotype 1, regardless of viral load, had a lower  
128 response rate to PEGASYS in combination with COPEGUS compared to patients with  
129 other viral genotypes.

130 **Table 1 Sustained Virologic Response (SVR) to Combination**  
131 **Therapy (Study NV15801\*)**

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

132  
133 Difference in overall treatment response (PEGASYS/COPEGUS – Interferon alfa-2b/ribavirin) was 9%  
134 (95% CI 2.3, 15.3).

135 \* Described as Study 4 in the PEGASYS Package Insert.

136  
137 In Study NV15942 (described as Study 5 in the PEGASYS Package Insert), all patients  
138 received PEGASYS 180 µg sc qw and were randomized to treatment for either 24 or 48  
139 weeks and to a COPEGUS dose of either 800 mg or 1000 mg/1200 mg (for body weight  
140 <75 kg/≥75 kg). Assignment to the four treatment arms was stratified by viral genotype  
141 and baseline HCV viral titer. Patients with genotype 1 and high viral titer (defined as >2

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142 x 10<sup>6</sup> HCV RNA copies/mL serum) were preferentially assigned to treatment for 48  
143 weeks.

### 144 HCV Genotypes

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

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

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

154 **Table 2 Sustained Virologic Response as a Function of Genotype**  
155 **(Study NV15942\*)**

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

156 \* Described as Study 5 in the PEGASYS Package Insert.

157 \*\*1000 mg for body weight <75 kg; 1200 mg for body weight ≥75 kg.

158

### 159 Other Treatment Response Predictors

160 Treatment response rates are lower in patients with poor prognostic factors receiving  
161 pegylated interferon alpha therapy. In studies NV15801 and NV15942, treatment  
162 response rates were lower in patients older than 40 years (50% vs. 66%), in patients with  
163 cirrhosis (47% vs. 59%), in patients weighing over 85 kg (49% vs. 60%), and in patients  
164 with genotype 1 with high vs. low viral load (43% vs. 56%). African-American patients  
165 had lower response rates compared to Caucasians.

166 Paired liver biopsies were performed on approximately 20% of patients in studies  
167 NV15801 and NV15942. Modest reductions in inflammation compared to baseline were  
168 seen in all treatment groups.

169 In studies NV15801 and NV15942, lack of early virologic response by 12 weeks (defined  
170 as HCV RNA undetectable or >2log<sub>10</sub> lower than baseline) was grounds for

171 discontinuation of treatment. Of patients who lacked an early viral response by 12 weeks  
 172 and completed a recommended course of therapy despite a protocol-defined option to  
 173 discontinue therapy, 5/39 (13%) achieved an SVR. Of patients who lacked an early viral  
 174 response by 24 weeks, 19 completed a full course of therapy and none achieved an SVR.

### 175 **CHC and Coinfection with HIV (CHC/HIV): Study NR15961**

176 In Study NR15961 (described as Study 6 in the PEGASYS Package Insert), patients with  
 177 CHC/HIV were randomized to receive either PEGASYS 180 µg sc once weekly (qw)  
 178 plus an oral placebo, PEGASYS 180 µg qw plus COPEGUS 800 mg po daily or  
 179 ROFERON®-A (interferon alfa-2a), 3 MIU sc tiw plus COPEGUS 800 mg po daily. All  
 180 patients received 48 weeks of therapy and sustained virologic response (SVR) was  
 181 assessed at 24 weeks of treatment-free follow-up. COPEGUS or placebo treatment  
 182 assignment was blinded in the PEGASYS treatment arms. All patients were adults, had  
 183 compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic  
 184 hepatitis C, and were previously untreated with interferon. Patients also had CD4+ cell  
 185 count ≥200 cells/µL or CD4+ cell count ≥100 cells/µL but <200 cells/µL and HIV-1  
 186 RNA <5000 copies/mL, and stable status of HIV. Approximately 15% of patients in the  
 187 study had cirrhosis. Results are shown in [Table 3](#).

188 **Table 3 Sustained Virologic Response in Patients With Chronic**  
 189 **Hepatitis C Coinfected With HIV (Study NR15961\*)**

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

190 \*PEGASYS + COPEGUS vs. PEGASYS; PEGASYS + COPEGUS vs. ROFERON-A + COPEGUS p-  
 191 value <0.0001 (Cochran-Mantel-Haenszel).  
 192

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

198 Of the patients who did not demonstrate either undetectable HCV RNA or at least a  
 199 2log<sub>10</sub> reduction from baseline in HCV RNA titer by 12 weeks of PEGASYS and  
 200 COPEGUS combination therapy, 2% (2/85) achieved an SVR.

201 In CHC patients with HIV coinfection who received 48 weeks of PEGASYS alone or in  
 202 combination with COPEGUS treatment, mean and median HIV RNA titers did not  
 203 increase above baseline during treatment or 24 weeks posttreatment.

204 **INDICATIONS AND USAGE**

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

212 **CONTRAINDICATIONS**

213 COPEGUS (ribavirin) is contraindicated in:

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

218 COPEGUS and PEGASYS combination therapy is contraindicated in patients with:

- 219 • Autoimmune hepatitis.  
220 • Hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic  
221 CHC monoinfected patients before or during treatment.  
222 • Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic  
223 CHC patients coinfecting with HIV before or during treatment.

224 **WARNINGS**

225 **COPEGUS must not be used alone because ribavirin monotherapy is not effective**  
226 **for the treatment of chronic hepatitis C virus infection. The safety and efficacy of**  
227 **COPEGUS have only been established when used together with PEGASYS**  
228 **(pegylated interferon alfa-2a, recombinant).**

229 COPEGUS and PEGASYS should be discontinued in patients who develop evidence of  
230 hepatic decompensation during treatment.

231 **There are significant adverse events caused by COPEGUS/PEGASYS therapy,**  
232 **including severe depression and suicidal ideation, hemolytic anemia, suppression of**  
233 **bone marrow function, autoimmune and infectious disorders, pulmonary**  
234 **dysfunction, pancreatitis, and diabetes. The PEGASYS Package Insert and**  
235 **MEDICATION GUIDE should be reviewed in their entirety prior to initiation of**  
236 **combination treatment for additional safety information.**

237 **General**

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

**241 Pregnancy**

242 **Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care**  
243 **must be taken to avoid pregnancy in female patients and in female partners of male**  
244 **patients. Ribavirin has demonstrated significant teratogenic and/or embryocidal**  
245 **effects in all animal species in which adequate studies have been conducted. These**  
246 **effects occurred at doses as low as one twentieth of the recommended human dose of**  
247 **ribavirin. COPEGUS THERAPY SHOULD NOT BE STARTED UNLESS A**  
248 **REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED**  
249 **IMMEDIATELY PRIOR TO PLANNED INITIATION OF THERAPY. Patients**  
250 **should be instructed to use at least two forms of effective contraception during**  
251 **treatment and for 6 months after treatment has been stopped. Pregnancy testing**  
252 **should occur monthly during COPEGUS therapy and for 6 months after therapy**  
253 **has stopped (see [CONTRAINDICATIONS](#) and [PRECAUTIONS: Information for](#)**  
254 **[Patients and Pregnancy: Category X](#)).**

**255 Anemia**

256 **The primary toxicity of ribavirin is hemolytic anemia (hemoglobin <10 g/dL), which**  
257 **was observed in approximately 13% of all COPEGUS and PEGASYS treated**  
258 **patients in clinical trials (see [PRECAUTIONS: Laboratory Tests](#)). The anemia**  
259 **associated with COPEGUS occurs within 1 to 2 weeks of initiation of therapy.**  
260 **BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT**  
261 **IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED**  
262 **PRETREATMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY OR MORE**  
263 **FREQUENTLY IF CLINICALLY INDICATED. Patients should then be followed**  
264 **as clinically appropriate.**

265 **Fatal and nonfatal myocardial infarctions have been reported in patients with**  
266 **anemia caused by ribavirin. Patients should be assessed for underlying cardiac**  
267 **disease before initiation of ribavirin therapy. Patients with pre-existing cardiac**  
268 **disease should have electrocardiograms administered before treatment, and should**  
269 **be appropriately monitored during therapy. If there is any deterioration of**  
270 **cardiovascular status, therapy should be suspended or discontinued (see [DOSAGE](#)**  
271 **AND ADMINISTRATION: COPEGUS Dosage Modification Guidelines). Because**  
272 **cardiac disease may be worsened by drug induced anemia, patients with a history of**  
273 **significant or unstable cardiac disease should not use COPEGUS (see [ADVERSE](#)**  
274 **[REACTIONS](#)).**

**275 Hepatic Failure**

276 **Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic**  
277 **decompensation and death when treated with alpha interferons, including PEGASYS.**  
278 **Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy**  
279 **(HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk**  
280 **for the development of hepatic decompensation compared to patients not receiving**  
281 **HAART. In Study NR15961 (described as Study 6 in the PEGASYS Package Insert),**  
282 **among 129 CHC/HIV cirrhotic patients receiving HAART, 14 (11%) of these patients**  
283 **across all treatment arms developed hepatic decompensation resulting in 6 deaths. All 14**  
284 **patients were on NRTIs, including stavudine, didanosine, abacavir, zidovudine, and**

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285 lamivudine. These small numbers of patients do not permit discrimination between  
286 specific NRTIs or the associated risk. During treatment, patients' clinical status and  
287 hepatic function should be closely monitored, and PEGASYS treatment should be  
288 immediately discontinued if decompensation (Child-Pugh score  $\geq 6$ ) is observed (see  
289 **CONTRAINDICATIONS**).

### 290 **Hypersensitivity**

291 Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction,  
292 and anaphylaxis) have been rarely observed during alpha interferon and ribavirin therapy.  
293 If such reaction occurs, therapy with PEGASYS and COPEGUS should be discontinued  
294 and appropriate medical therapy immediately instituted. Serious skin reactions including  
295 vesiculobullous eruptions, reactions in the spectrum of Stevens Johnson Syndrome  
296 (erythema multiforme major) with varying degrees of skin and mucosal involvement and  
297 exfoliative dermatitis (erythroderma) have been rarely reported in patients receiving  
298 PEGASYS with and without ribavirin. Patients developing signs or symptoms of severe  
299 skin reactions must discontinue therapy (see **ADVERSE REACTIONS: Postmarketing**  
300 **Experience**).

### 301 **Pulmonary**

302 Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and  
303 occasional cases of fatal pneumonia, have been reported during therapy with ribavirin  
304 and interferon. In addition, sarcoidosis or the exacerbation of sarcoidosis has been  
305 reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment,  
306 the patient should be closely monitored and, if appropriate, combination  
307 COPEGUS/PEGASYS treatment should be discontinued.

### 308 **Other**

309 COPEGUS and PEGASYS therapy should be suspended in patients with signs and  
310 symptoms of pancreatitis, and discontinued in patients with confirmed pancreatitis.

311 COPEGUS should not be used in patients with creatinine clearance  $< 50$  mL/min (see  
312 **CLINICAL PHARMACOLOGY: Special Populations**).

313 COPEGUS must be discontinued immediately and appropriate medical therapy instituted  
314 if an acute hypersensitivity reaction (e.g., urticaria, angioedema, bronchoconstriction,  
315 anaphylaxis) develops. Transient rashes do not necessitate interruption of treatment.

### 316 **PRECAUTIONS**

317 The safety and efficacy of COPEGUS and PEGASYS therapy for the treatment of  
318 adenovirus, RSV, parainfluenza or influenza infections have not been established.  
319 COPEGUS should not be used for these indications. Ribavirin for inhalation has a  
320 separate package insert, which should be consulted if ribavirin inhalation therapy is being  
321 considered.

322 The safety and efficacy of COPEGUS and PEGASYS therapy have not been established  
323 in liver or other organ transplant patients, patients with decompensated liver disease due  
324 to hepatitis C virus infection, patients who are non-responders to interferon therapy or  
325 patients coinfecting with HBV or HIV and a CD4+ cell count  $< 100$  cells/ $\mu$ L.

**326 Information for Patients**

327 Patients must be informed that ribavirin may cause birth defects and/or death of the  
328 exposed fetus. COPEGUS therapy must not be used by women who are pregnant or by  
329 men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy  
330 in female patients and in female partners of male patients taking COPEGUS therapy and  
331 for 6 months posttherapy. COPEGUS therapy should not be initiated until a report of a  
332 negative pregnancy test has been obtained immediately prior to initiation of therapy.  
333 Patients must perform a pregnancy test monthly during therapy and for 6 months  
334 posttherapy.

335 Female patients of childbearing potential and male patients with female partners of  
336 childbearing potential must be advised of the teratogenic/embryocidal risks and must be  
337 instructed to practice effective contraception during COPEGUS therapy and for 6 months  
338 posttherapy. Patients should be advised to notify the healthcare provider immediately in  
339 the event of a pregnancy (see **CONTRAINDICATIONS** and **WARNINGS**).

340 The most common adverse event associated with ribavirin is anemia, which may be severe  
341 (see **ADVERSE REACTIONS**). Patients should be advised that laboratory evaluations  
342 are required prior to starting COPEGUS therapy and periodically thereafter (see  
343 **Laboratory Tests**). It is advised that patients be well hydrated, especially during the  
344 initial stages of treatment.

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

347 Patients should be informed regarding the potential benefits and risks attendant to the use  
348 of COPEGUS. Instructions on appropriate use should be given, including review of the  
349 contents of the enclosed **MEDICATION GUIDE**, which is not a disclosure of all or  
350 possible adverse effects.

351 Patients should be advised to take COPEGUS with food.

**352 Laboratory Tests**

353 Before beginning COPEGUS therapy, standard hematological and biochemical  
354 laboratory tests must be conducted for all patients. Pregnancy screening for women of  
355 childbearing potential must be done.

356 After initiation of therapy, hematological tests should be performed at 2 weeks and 4  
357 weeks and biochemical tests should be performed at 4 weeks. Additional testing should  
358 be performed periodically during therapy. Monthly pregnancy testing should be done  
359 during combination therapy and for 6 months after discontinuing therapy.

360 The entrance criteria used for the clinical studies of COPEGUS and PEGASYS  
361 combination therapy may be considered as a guideline to acceptable baseline values for  
362 initiation of treatment:

- 363 • Platelet count  $\geq 90,000$  cells/mm<sup>3</sup> (as low as 75,000 cells/mm<sup>3</sup> in patients with  
364 cirrhosis or 70,000 cells/mm<sup>3</sup> in patients with CHC and HIV)
- 365 • Absolute neutrophil count (ANC)  $\geq 1500$  cells/mm<sup>3</sup>

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- 366 • TSH and T<sub>4</sub> within normal limits or adequately controlled thyroid function
- 367 • ECG (see **WARNINGS**)
- 368 • CD4+ cell count ≥200 cells/μL or CD4+ cell count ≥100 cells/μL but <200 cells/μL
- 369 and HIV-1 RNA <5000 copies/mL in patients coinfecting with HIV
- 370 • Hemoglobin ≥12 g/dL for women and ≥13 g/dL for men in CHC monoinfected
- 371 patients
- 372 • Hemoglobin ≥11 g/dL for women and ≥12 g/dL for men in patients with CHC and
- 373 HIV

374 The maximum drop in hemoglobin usually occurred during the first 8 weeks of initiation  
375 of COPEGUS therapy. Because of this initial acute drop in hemoglobin, it is advised that  
376 a complete blood count should be obtained pretreatment and at week 2 and week 4 of  
377 therapy or more frequently if clinically indicated. Additional testing should be performed  
378 periodically during therapy. Patients should then be followed as clinically appropriate.

### 379 **Drug Interactions**

380 Results from a pharmacokinetic sub-study demonstrated no pharmacokinetic interaction  
381 between PEGASYS (peginterferon alfa-2a) and ribavirin.

### 382 **Nucleoside Analogues**

#### 383 *NRTIs*

384 In Study NR15961 among the CHC/HIV coinfecting cirrhotic patients receiving NRTIs  
385 cases of hepatic decompensation (some fatal) were observed (see **WARNINGS: Hepatic**  
386 **Failure**).

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

#### 393 *Didanosine*

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

#### 398 *Zidovudine*

399 In Study NR15961, patients who were administered zidovudine in combination with  
400 PEGASYS/COPEGUS developed severe neutropenia (ANC <500) and severe anemia  
401 (hemoglobin <8 g/dL) more frequently than similar patients not receiving zidovudine  
402 (neutropenia 15% vs. 9%) (anemia 5% vs. 1%).

403 *Lamivudine, Stavudine, and Zidovudine*

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

409 **Carcinogenesis, Mutagenesis, Impairment of Fertility**410 **Carcinogenesis**

411 In a p53 (+/-) mouse carcinogenicity study and a rat 2-year carcinogenicity study at doses  
412 up to the maximum tolerated doses of 100 mg/kg/day and 60 mg/kg/day, respectively,  
413 ribavirin was not oncogenic. On a body surface area basis, these doses are approximately  
414 0.5 and 0.6 times the maximum recommended human 24-hour dose of ribavirin.

415 **Mutagenesis**

416 Ribavirin demonstrated mutagenic activity in the in vitro mouse lymphoma assay. No  
417 clastogenic activity was observed in an in vivo mouse micronucleus assay at doses up to  
418 2000 mg/kg. However, results from studies published in the literature show clastogenic  
419 activity in the in vivo mouse micronucleus assay at oral doses up to 2000 mg/kg. A  
420 dominant lethal assay in rats was negative, indicating that if mutations occurred in rats  
421 they were not transmitted through male gametes. However, potential carcinogenic risk to  
422 humans cannot be excluded.

423 **Impairment of Fertility**

424 In a fertility study in rats, ribavirin showed a marginal reduction in sperm counts at the  
425 dose of 100 mg/kg/day with no effect on fertility. Upon cessation of treatment, total  
426 recovery occurred after 1 spermatogenesis cycle. Abnormalities in sperm were observed  
427 in studies in mice designed to evaluate the time course and reversibility of ribavirin-  
428 induced testicular degeneration at doses of 15 to 150 mg/kg/day (approximately 0.1 to 0.8  
429 times the maximum recommended human 24-hour dose of ribavirin) administered for 3  
430 to 6 months. Upon cessation of treatment, essentially total recovery from ribavirin-  
431 induced testicular toxicity was apparent within 1 or 2 spermatogenic cycles.

432 Female patients of childbearing potential and male patients with female partners of  
433 childbearing potential should not receive COPEGUS unless the patient and his/her  
434 partner are using effective contraception (two reliable forms). Based on a multiple dose  
435 half-life ( $t_{1/2}$ ) of ribavirin of 12 days, effective contraception must be utilized for 6  
436 months posttherapy (i.e., 15 half-lives of clearance for ribavirin).

437 No reproductive toxicology studies have been performed using PEGASYS in  
438 combination with COPEGUS. However, peginterferon alfa-2a and ribavirin when  
439 administered separately, each has adverse effects on reproduction. It should be assumed  
440 that the effects produced by either agent alone would also be caused by the combination  
441 of the two agents.

**442 Pregnancy**

443 Pregnancy: Category X (see **CONTRAINDICATIONS**)

444 Ribavirin produced significant embryocidal and/or teratogenic effects in all animal  
445 species in which adequate studies have been conducted. Malformations of the skull,  
446 palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and  
447 severity of teratogenic effects increased with escalation of the drug dose. Survival of  
448 fetuses and offspring was reduced.

449 In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no-  
450 effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for  
451 both the rat and rabbit; approximately 0.06 times the recommended human 24-hour dose  
452 of ribavirin). No maternal toxicity or effects on offspring were observed in a  
453 peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (approximately 0.01  
454 times the maximum recommended human 24-hour dose of ribavirin).

**455 *Treatment and Posttreatment: Potential Risk to the Fetus***

456 Ribavirin is known to accumulate in intracellular components from where it is cleared  
457 very slowly. It is not known whether ribavirin is contained in sperm, and if so, will exert  
458 a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was  
459 concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg  
460 for 5 days (up to 1.7 times the maximum recommended human dose of ribavirin).  
461 However, because of the potential human teratogenic effects of ribavirin, male patients  
462 should be advised to take every precaution to avoid risk of pregnancy for their female  
463 partners.

464 COPEGUS should not be used by pregnant women or by men whose female partners are  
465 pregnant. Female patients of childbearing potential and male patients with female  
466 partners of childbearing potential should not receive COPEGUS unless the patient and  
467 his/her partner are using effective contraception (two reliable forms) during therapy and  
468 for 6 months posttherapy.

**469 *Ribavirin Pregnancy Registry***

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

**474 *Animal Toxicology***

475 Long-term study in the mouse and rat (18 to 24 months; dose 20 to 75, and 10 to 40  
476 mg/kg/day, respectively, approximately 0.1 to 0.4 times the maximum human daily dose  
477 of ribavirin) have demonstrated a relationship between chronic ribavirin exposure and an  
478 increased incidence of vascular lesions (microscopic hemorrhages) in mice. In rats,  
479 retinal degeneration occurred in controls, but the incidence was increased in ribavirin-  
480 treated rats.

**481 Nursing Mothers**

482 It is not known whether ribavirin is excreted in human milk. Because many drugs are  
483 excreted in human milk and to avoid any potential for serious adverse reactions in  
484 nursing infants from ribavirin, a decision should be made either to discontinue nursing or  
485 therapy with COPEGUS, based on the importance of the therapy to the mother.

**486 Pediatric Use**

487 Safety and effectiveness of COPEGUS have not been established in patients below the  
488 age of 18.

**489 Geriatric Use**

490 Clinical studies of COPEGUS and PEGASYS did not include sufficient numbers of  
491 subjects aged 65 or over to determine whether they respond differently from younger  
492 subjects. Specific pharmacokinetic evaluations for ribavirin in the elderly have not been  
493 performed. The risk of toxic reactions to this drug may be greater in patients with  
494 impaired renal function. COPEGUS should not be administered to patients with  
495 creatinine clearance <50 mL/min. (see **CLINICAL PHARMACOLOGY: Special**  
496 **Populations**).

**497 Effect of Gender**

498 No clinically significant differences in the pharmacokinetics of ribavirin were observed  
499 between male and female subjects.

**500 ADVERSE REACTIONS**

501 PEGASYS in combination with COPEGUS causes a broad variety of serious adverse  
502 reactions (see **BOXED WARNING** and **WARNINGS**).

503 The most common life-threatening or fatal events induced or aggravated by PEGASYS  
504 and COPEGUS were depression, suicide, relapse of drug abuse/overdose, and bacterial  
505 infections, each occurring at a frequency of <1%. Hepatic decompensation occurred in  
506 2% (10/574) of CHC/HIV patients (see **WARNINGS: Hepatic Failure**).

507 In all studies, one or more serious adverse reactions occurred in 10% of CHC  
508 monoinfected patients and in 19% of CHC/HIV patients receiving PEGASYS alone or in  
509 combination with COPEGUS. The most common serious adverse event (3% in CHC and  
510 5% in CHC/HIV) was bacterial infection (e.g., sepsis, osteomyelitis, endocarditis,  
511 pyelonephritis, pneumonia). Other SAEs occurred at a frequency of <1% and included:  
512 suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose,  
513 angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus,  
514 autoimmune phenomena (e.g., hyperthyroidism, hypothyroidism, sarcoidosis, systemic  
515 lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic  
516 ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism,  
517 coma, myositis, cerebral hemorrhage, thrombotic thrombocytopenic purpura, psychotic  
518 disorder, and hallucination.

519 Nearly all patients in clinical trials experienced one or more adverse events. The most  
520 commonly reported adverse reactions were psychiatric reactions, including depression,  
521 insomnia, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia,

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522 headache and rigors. Other common reactions were anorexia, nausea and vomiting,  
523 diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

524 Ten percent of CHC monoinfected patients receiving 48 weeks of therapy with  
525 PEGASYS in combination with COPEGUS discontinued therapy; 16% of CHC/HIV  
526 coinfecting patients discontinued therapy. The most common reasons for discontinuation  
527 of therapy were psychiatric, flu-like syndrome (e.g., lethargy, fatigue, headache),  
528 dermatologic and gastrointestinal disorders and laboratory abnormalities  
529 (thrombocytopenia, neutropenia, and anemia).

530 Overall 39% of patients with CHC or CHC/HIV required modification of PEGASYS  
531 and/or COPEGUS therapy. The most common reason for dose modification of  
532 PEGASYS in CHC and CHC/HIV patients was for laboratory abnormalities; neutropenia  
533 (20% and 27%, respectively) and thrombocytopenia (4% and 6%, respectively). The most  
534 common reason for dose modification of COPEGUS in CHC and CHC/HIV patients was  
535 anemia (22% and 16%, respectively).

536 PEGASYS dose was reduced in 12% of patients receiving 1000 mg to 1200 mg  
537 COPEGUS for 48 weeks and in 7% of patients receiving 800 mg COPEGUS for 24  
538 weeks. COPEGUS dose was reduced in 21% of patients receiving 1000 mg to 1200 mg  
539 COPEGUS for 48 weeks and in 12% of patients receiving 800 mg COPEGUS for 24  
540 weeks.

541 Chronic hepatitis C monoinfected patients treated for 24 weeks with PEGASYS and  
542 800 mg COPEGUS were observed to have lower incidence of serious adverse events (3%  
543 vs. 10%), hemoglobin <10g/dL (3% vs. 15%), dose modification of PEGASYS (30% vs.  
544 36%) and COPEGUS (19% vs. 38%), and of withdrawal from treatment (5% vs. 15%)  
545 compared to patients treated for 48 weeks with PEGASYS and 1000 mg or 1200 mg  
546 COPEGUS. On the other hand, the overall incidence of adverse events appeared to be  
547 similar in the two treatment groups.

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

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**Table 4 Adverse Reactions Occurring in ≥5% of Patients in Chronic Hepatitis C Clinical Trials (Study NV15801\*)**

Body System	CHC Combination Therapy Study NV15801	
	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week	Intron A + 1000 mg or 1200 mg Rebetol® 48 week
	N=451	N=443
	%	%
<b>Application Site Disorders</b>		
Injection site reaction	23	16
<b>Endocrine Disorders</b>		
Hypothyroidism	4	5
<b>Flu-like Symptoms and Signs</b>		
Fatigue/Asthenia	65	68
Pyrexia	41	55
Rigors	25	37
Pain	10	9
<b>Gastrointestinal</b>		
Nausea/Vomiting	25	29
Diarrhea	11	10
Abdominal pain	8	9
Dry mouth	4	7
Dyspepsia	6	5
<b>Hematologic**</b>		
Lymphopenia	14	12
Anemia	11	11
Neutropenia	27	8
Thrombocytopenia	5	<1
<b>Metabolic and Nutritional</b>		
Anorexia	24	26
Weight decrease	10	10
<b>Musculoskeletal, Connective Tissue and Bone</b>		
Myalgia	40	49
Arthralgia	22	23

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<b>Body System</b>	<b>CHC Combination Therapy Study NV15801</b>	
	<b>PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 week</b>	<b>Intron A + 1000 mg or 1200 mg Rebetol® 48 week</b>
	<b>N=451</b>	<b>N=443</b>
	<b>%</b>	<b>%</b>
Back pain	5	5
<b>Neurological</b>		
Headache	43	49
Dizziness (excluding vertigo)	14	14
Memory impairment	6	5
<b>Psychiatric</b>		
Irritability/Anxiety/Nervousness	33	38
Insomnia	30	37
Depression	20	28
Concentration impairment	10	13
Mood alteration	5	6
<b>Resistance Mechanism Disorders</b>		
Overall	12	10
<b>Respiratory, Thoracic and Mediastinal</b>		
Dyspnea	13	14
Cough	10	7
Dyspnea exertional	4	7
<b>Skin and Subcutaneous Tissue</b>		
Alopecia	28	33
Pruritus	19	18
Dermatitis	16	13
Dry skin	10	13
Rash	8	5
Sweating increased	6	5
Eczema	5	4
<b>Visual Disorders</b>		
Vision blurred	5	2

555

\* Described as Study 4 in the PEGASYS Package Insert.

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556 \*\* Severe hematologic abnormalities (lymphocyte  $<0.5 \times 10^9/L$ ; hemoglobin  $<10 \text{ g/dL}$ ; neutrophil  $<0.75 \times$   
557  $10^9/L$ ; platelet  $<50 \times 10^9/L$ ).

### 558 **Common Adverse Reactions in CHC With HIV Coinfection**

559 The adverse event profile of coinfecting patients treated with PEGASYS and COPEGUS  
560 in Study NR15961 was generally similar to that shown for mono-infected patients in  
561 Study NV15801 (**Table 4**). Events occurring more frequently in coinfecting patients were  
562 neutropenia (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%), and  
563 mood alteration (9%).

### 564 **Laboratory Test Values**

565 Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Anemia  
566 (hemoglobin  $<10 \text{ g/dL}$ ) was observed in 13% of all COPEGUS and PEGASYS  
567 combination-treated patients in clinical trials. The maximum drop in hemoglobin  
568 occurred during the first 8 weeks of initiation of ribavirin therapy (see **DOSAGE AND**  
569 **ADMINISTRATION: Dose Modifications**).

### 570 **Postmarketing Experience**

571 The following adverse reactions have been identified and reported during post-approval  
572 use of PEGASYS therapy: dehydration, hearing impairment, hearing loss, serious skin  
573 reactions (see **WARNINGS: Hypersensitivity**), and serous retinal detachment.  
574 Additionally, pure red cell aplasia (PRCA) has been reported with COPEGUS in  
575 combination with PEGASYS.

### 576 **OVERDOSAGE**

577 No cases of overdose with COPEGUS have been reported in clinical trials. Hypocalcemia  
578 and hypomagnesemia have been observed in persons administered greater than the  
579 recommended dosage of ribavirin. In most of these cases, ribavirin was administered  
580 intravenously at dosages up to and in some cases exceeding four times the recommended  
581 maximum oral daily dose.

## 582 **DOSAGE AND ADMINISTRATION**

### 583 **CHC Mono-infection**

584 The recommended dose of COPEGUS tablets is provided in **Table 5**. The recommended  
585 duration of treatment for patients previously untreated with ribavirin and interferon is 24  
586 to 48 weeks.

587 The daily dose of COPEGUS is 800 mg to 1200 mg administered orally in two divided  
588 doses. The dose should be individualized to the patient depending on baseline disease  
589 characteristics (e.g., genotype), response to therapy, and tolerability of the regimen (see  
590 **Table 5**).

591 In the pivotal clinical trials, patients were instructed to take COPEGUS with food;  
592 therefore, patients are advised to take COPEGUS with food.

593 **Table 5 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

594 Genotypes non-1 showed no increased response to treatment beyond 24 weeks (see [Table 2](#)).

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

596 **CHC with HIV Coinfection**

597 The recommended dose for hepatitis C in HCV/HIV coinfecting patients is PEGASYS  
598 180 µg sc once weekly and COPEGUS 800 mg po daily for a total of 48 weeks,  
599 regardless of genotype.

600 **Dose Modifications**

601 **If severe adverse reactions or laboratory abnormalities develop during combination**  
602 **COPEGUS/PEGASYS therapy, the dose should be modified or discontinued, if**  
603 **appropriate, until the adverse reactions abate. If intolerance persists after dose**  
604 **adjustment, COPEGUS/PEGASYS therapy should be discontinued.**

605 COPEGUS should be administered with caution to patients with pre-existing cardiac  
606 disease (see [Table 6](#)). Patients should be assessed before commencement of therapy and  
607 should be appropriately monitored during therapy. If there is any deterioration of  
608 cardiovascular status, therapy should be stopped (see [WARNINGS](#)).

609 **Table 6 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

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

611 Once COPEGUS has been withheld due to either a laboratory abnormality or clinical  
612 manifestation, an attempt may be made to restart COPEGUS at 600 mg daily and further  
613 increase the dose to 800 mg daily depending upon the physician's judgment. However, it  
614 is not recommended that COPEGUS be increased to its original assigned dose (1000 mg  
615 to 1200 mg).

616 **Renal Impairment**

617 COPEGUS should not be used in patients with creatinine clearance <50 mL/min (see  
618 [WARNINGS](#) and [CLINICAL PHARMACOLOGY: Special Populations](#)).

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### 619 **HOW SUPPLIED**

620 COPEGUS<sup>®</sup> (ribavirin) is available as tablets for oral administration. Each tablet contains  
621 200 mg of ribavirin and is light pink to pink colored, flat, oval-shaped, film-coated, and  
622 engraved with RIB 200 on one side and ROCHE on the other side. They are packaged as  
623 bottle of 168 tablets (NDC 0004-0086-94).

### 624 **Storage Conditions**

625 Store the COPEGUS<sup>®</sup> Tablets bottle at 25°C (77°F); excursions are permitted between  
626 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep bottle  
627 tightly closed.

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

629 PI Revised: March 2010

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631

**MEDICATION GUIDE**

632

**COPEGUS®**

633

**(ribavirin, USP)**

634

**TABLETS**

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Read this Medication Guide carefully before you start taking COPEGUS (Co-PEG-UHS) and read the Medication Guide each time you get more COPEGUS. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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**What is the most important information I should know about COPEGUS?**

640

**1. COPEGUS, a form of ribavirin, may cause birth defects or death of an unborn child. Therefore, if you are pregnant or your partner is pregnant or plans to become pregnant, do not take COPEGUS.** Female patients and female partners of male patients being treated with COPEGUS must not become pregnant during treatment and for 6 months after treatment has stopped.

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**During this time you must have pregnancy tests that show you are not pregnant. You must also use 2 effective forms of birth control during therapy and for 6 months after stopping therapy.** Male patients should use a condom with spermicide as one of the two forms.

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If pregnancy occurs, report the pregnancy to your healthcare provider right away. (See “**What should I avoid while taking COPEGUS?**”.)

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

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**2. COPEGUS can cause a dangerous drop in your red blood cell count.** COPEGUS can cause anemia, which is a decrease in the number of red blood cells. This can be dangerous, especially if you have heart or breathing problems. This may cause a worsening of heart (cardiovascular) or circulatory problems. Some patients may get chest pain and rarely, a heart attack. Patients with a history of heart disease have the highest chance of this. Tell your healthcare provider, before taking COPEGUS if you have or have ever had any heart or breathing problems. Your healthcare provider should check your red blood cell count before you start treatment with COPEGUS and often during the first 4 weeks of treatment. Your red blood cell count may be done more often if you have any heart or breathing problems.

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**3. Do not take COPEGUS alone to treat hepatitis C virus infection.** COPEGUS does not treat hepatitis C virus infections by itself. COPEGUS should be used in combination with PEGASYS® (peginterferon alfa-2a) to treat continuing (chronic) hepatitis C virus infections. You should read the Medication Guide for PEGASYS

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670 because it has additional important information about treatment that is not covered in  
671 this Medication Guide. Your healthcare provider or pharmacist should give you a  
672 copy of the PEGASYS Medication Guide.

### 673 **What is COPEGUS?**

674 COPEGUS is the antiviral medicine ribavirin. It is used in combination with a medicine  
675 called PEGASYS (peginterferon alfa-2a) to treat some adults with chronic hepatitis C  
676 whose liver still works normally, and who have not been treated before with a medicine  
677 called an interferon alpha. It is not known how COPEGUS and PEGASYS work together  
678 to fight hepatitis C virus infections.

679 It is not known if treatment with COPEGUS and PEGASYS combination therapy can  
680 cure hepatitis C or if it can prevent liver damage (cirrhosis), liver failure or liver cancer  
681 that is caused by hepatitis C virus infections. It is not known if treatment with COPEGUS  
682 and PEGASYS combination therapy will prevent an infected person from spreading the  
683 hepatitis C virus to another person.

684 Treatment with COPEGUS has not been studied in children under 18 years of age.

### 685 **Who should not take COPEGUS?**

686 **Do not use COPEGUS if:**

- 687 • **You are a female and you are pregnant or plan to become pregnant** during  
688 treatment or during the 6 months after your treatment has ended. (See “**What is the**  
689 **most important information I should know about COPEGUS?**” and “**What**  
690 **should I avoid while taking COPEGUS?**”.)
- 691 • **You are a male patient with a female sexual partner who is pregnant or plans to**  
692 **become pregnant** at any time while you are being treated with COPEGUS or during  
693 the 6 months after your treatment has ended. (See “**What is the most important**  
694 **information I should know about COPEGUS?**” and “**What should I avoid while**  
695 **taking COPEGUS?**”.)
- 696 • **You are breast feeding. We do not know if COPEGUS can pass through your**  
697 **milk and if it can harm your baby. You will need to choose either to breast-feed**  
698 **or take COPEGUS, but not both.**
- 699 • **You have a liver disease called autoimmune hepatitis** (hepatitis caused by your  
700 immune system attacking your liver).
- 701 • **You have unstable or severe liver disease.**
- 702 • **You are allergic to any of the ingredients in COPEGUS.** The active ingredient in  
703 COPEGUS is ribavirin. See the end of this Medication Guide for a list of all the  
704 ingredients in COPEGUS.

705 **Tell your healthcare provider before starting treatment with COPEGUS in**  
706 **combination with PEGASYS (see also the PEGASYS Medication Guide) if you have**  
707 **any of the following medical conditions:**

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- 708 • **mental health problems, such as depression or anxiety:** COPEGUS and  
709 PEGASYS combination therapy may make them worse. Tell your healthcare provider  
710 if you are being treated or had treatment in the past for any mental problems,  
711 including depression, thoughts of ending your life (suicidal thoughts) or a feeling of  
712 loss of contact with reality, such as hearing voices or seeing things that are not there  
713 (psychosis). Tell your healthcare provider if you take any medicines for these  
714 problems.
- 715 • **high blood pressure, heart problems or have had a heart attack.** COPEGUS may  
716 worsen heart problems such as high blood pressure, increased heart rate, and chest  
717 pain. Tell your healthcare provider if you have or had a heart problem. Patients who  
718 have had certain heart problems should not take COPEGUS.
- 719 • **blood disorders,** including anemia (low red blood cell count), thalassemia  
720 (Mediterranean anemia) and sickle-cell anemia. COPEGUS can reduce the number of  
721 red blood cells you have. This may make you feel dizzy or weak and could worsen  
722 any heart problems you might have.
- 723 • **kidney problems.** If your kidneys do not work properly, you may have worse side  
724 effects from COPEGUS treatment and require a lower dose.
- 725 • **liver problems** (other than hepatitis C virus infection).
- 726 • **organ transplant,** and you are taking medicine that keeps your body from rejecting  
727 your transplant (suppresses your immune system).
- 728 • **thyroid disease.** COPEGUS and PEGASYS combination therapy may make your  
729 thyroid disease worse or harder to treat. COPEGUS and PEGASYS treatment may be  
730 stopped if you develop thyroid problems that cannot be controlled by medicine.
- 731 • **have or had drug or alcohol addiction or abuse.**
- 732 • **cancer.**
- 733 • **infection with hepatitis B virus.**
- 734 • **diabetes.** COPEGUS and PEGASYS combination therapy may make your diabetes  
735 worse or harder to treat.
- 736 • **past interferon treatment for hepatitis C virus infection that did not work for**  
737 **you.**
- 738 **Tell your healthcare provider about all the medicines you take,** including prescription  
739 and non-prescription medicines, vitamins or herbal supplements. Some medicines can  
740 cause serious side effects if taken while you also take COPEGUS. Some medicines may  
741 affect how COPEGUS works or COPEGUS may affect how your other medicines work.  
742 Be especially sure to tell your healthcare provider if you take any medicines to treat HIV.
- 743 **For more information see the PEGASYS Medication Guide.**

744 **How should I take COPEGUS?**

- 745 • Your healthcare provider will determine the right dose of COPEGUS based on your  
746 weight.
- 747 • Take COPEGUS 1 time in the morning and 1 time at night (2 times a day). Take  
748 COPEGUS the same 2 times each day.
- 749 • Take COPEGUS with food.
- 750 • It is very important to follow your dosing schedule and your healthcare provider’s  
751 instructions on how to take your medicines.
- 752 • Take COPEGUS for as long as it is prescribed, and do not take more than your  
753 healthcare provider prescribes.
- 754 • If you miss a dose of COPEGUS and remember **the same day**, take the missed dose  
755 as soon as you remember. If **the whole day has passed**, ask your healthcare provider  
756 what to do. Do not take 2 doses at the same time.
- 757 • Your healthcare provider may adjust your dose of COPEGUS based on blood tests  
758 that show your response to treatment and side effects you may have.
- 759 • **Females taking COPEGUS or female sexual partners of male patients taking**  
760 **COPEGUS must have a pregnancy test:**
- 761 • before treatment begins
- 762 • every month during treatment
- 763 • for 6 months after treatment ends to make sure there is no pregnancy

764 It is also important not to use other ribavirin medicines without talking to your healthcare  
765 provider. Please see the PEGASYS Medication Guide for the proper use of PEGASYS  
766 injection.

767 **What should I avoid while taking COPEGUS?**

768 **Avoid the following during COPEGUS treatment:**

- 769 • **Do not get pregnant.** If you or your sexual partner get pregnant during treatment  
770 with COPEGUS or in the 6 months after treatment ends, tell your healthcare provider  
771 right away. (See **“What is the most important information I should know about**  
772 **COPEGUS?”**.)
- 773 Talk with your healthcare provider about birth control methods and how to avoid  
774 pregnancy. You must use extreme care to avoid pregnancy during and for 6 months  
775 after treatment in female and male patients.
- 776 • **Do not take COPEGUS alone to treat your hepatitis C virus infection.**  
777 COPEGUS should be used in combination with PEGASYS (peginterferon alfa-2a) to  
778 treat chronic hepatitis C virus infections. (See **“What is the most important**  
779 **information I should know about COPEGUS?”**.)
- 780 • **Do not breast feed.** COPEGUS may pass through your milk and may harm your  
781 baby.
- 782 • **Do not drink alcohol**, including beer, wine, and liquor. This may make your liver  
783 disease worse.

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784 • **Do not drive or operate machinery** if COPEGUS makes you feel tired, dizzy or  
785 confused.

786 • **Do not take other medicines unless your healthcare provider knows about them.**  
787 Take only medicines prescribed or approved by your healthcare provider. These  
788 include prescription and non-prescription medicines, vitamins or herbal supplements.  
789 Talk to your healthcare provider before starting any new medicine.

### 790 **What are the possible side effects of COPEGUS?**

791 **The most serious possible side effects of COPEGUS are:**

792 • **Harm to unborn children.** COPEGUS may cause birth defects or death of an unborn  
793 child. (For more details, see “**What is the most important information I should**  
794 **know about COPEGUS?**”.)

795 • **Anemia.** Anemia is a reduction in the number of red blood cells you have. Anemia  
796 can be dangerous, especially if you have heart or breathing problems. Tell your  
797 healthcare provider right away if you feel tired, have chest pain or shortness of breath.  
798 These may be signs of low red blood cell counts.

799 • **Liver problems.** Some patients may develop worsening of liver function. Some of  
800 the symptoms may include stomach bloating, confusion, brown urine, and yellow  
801 eyes. Tell your healthcare provider immediately if any of these symptoms occur.

802 **Call your healthcare provider right away if you have any of the following symptoms.**  
803 **They may be signs of a serious side effect of COPEGUS and PEGASYS treatment.**

- 804 • trouble breathing
- 805 • hives or swelling
- 806 • chest pain
- 807 • severe stomach pain or low back pain
- 808 • bloody diarrhea or bloody stools (bowel movements). These may look like black tar.
- 809 • bruising or unusual bleeding
- 810 • change in your vision
- 811 • high fever (temperature greater than 100.5°F)
- 812 • you have psoriasis (a skin disease) and it gets worse
- 813 • you become very depressed or think about suicide (ending your life)
- 814 • Skin rash can occur in patients taking PEGASYS. In some patients a rash can be  
815 serious. If you develop a rash with fever, blisters, or sores in your mouth, nose or  
816 eyes or conjunctivitis (red or inflamed eyes, like “pink eye”), stop using PEGASYS  
817 and call your doctor right away

818  
819 **The most common side effects of COPEGUS are likely to be the same as for other**  
820 **ribavirin products. These are:**

- 821 • feeling tired
- 822 • nausea and appetite loss
- 823 • rash and itching
- 824 • cough

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825 These are not all the possible side effects of COPEGUS treatment. For more information,  
826 ask your doctor or pharmacist and see the PEGASYS Medication Guide. Call your doctor  
827 for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-  
828 1088. You may also report side effects to Genentech at 1-888-835-2555.

### 829 **What should I know about hepatitis C infection?**

830 Hepatitis C infection is a disease caused by a virus that infects the liver. Hepatitis C is  
831 more serious for some people than others. Most people who get hepatitis C carry the virus  
832 in their blood for the rest of their lives. Most of these people will have some liver  
833 damage, but many do not feel sick from the disease. In some people, the liver becomes  
834 badly damaged and scarred. This is called cirrhosis. Cirrhosis can cause the liver to stop  
835 working. Some people may get liver cancer or liver failure from the hepatitis C virus.

836 Hepatitis C virus is spread from one person to another by contact with an infected  
837 person's blood. You should talk to your healthcare provider about ways to prevent you  
838 from infecting others.

### 839 **How should I store COPEGUS?**

840 Store COPEGUS tablets at room temperature (77°F).

841 Please refer to the PEGASYS Medication Guide for storage information about  
842 PEGASYS injection.

### 843 **General information about the safe and effective use of COPEGUS**

844 Medicines are sometimes prescribed for purposes other than those listed in a Medication  
845 Guide. Do not use COPEGUS for a condition for which it was not prescribed. Do not  
846 give COPEGUS to other people, even if they have the same symptoms that you have.

847 This Medication Guide summarizes the most important information about COPEGUS. If  
848 you would like more information, talk with your healthcare provider. You can ask your  
849 healthcare provider or pharmacist for information about COPEGUS that is written for  
850 healthcare professionals.

### 851 **What are the ingredients in COPEGUS?**

852 Active Ingredient: ribavirin

853 Inactive Ingredients: The core of the tablet contains corn starch, magnesium stearate,  
854 microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. The  
855 coating of the tablet contains ethyl cellulose (200 mg tablet only), hydroxypropylmethyl  
856 cellulose, red iron oxide, talc, titanium dioxide, triacetin, and yellow iron oxide.

857  
858 This Medication Guide has been approved by the US Food and Drug Administration.

859 MG Revised: January 2010

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