



**COPEGUS®**  
**(ribavirin, USP)**  
**TABLETS**

**R<sub>x</sub> only**

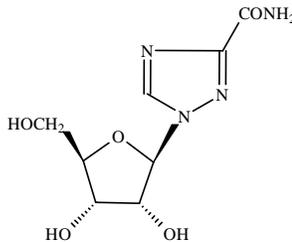
**COPEGUS (ribavirin) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication (see WARNINGS).**

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



## COPEGUS® (ribavirin, USP)

31 The empirical formula of ribavirin is  $C_8H_{12}N_4O_5$  and the molecular weight is 244.2.  
32 Ribavirin is a white to off-white powder. It is freely soluble in water and slightly soluble  
33 in anhydrous alcohol.

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

### 41 Mechanism of Action

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

## 45 CLINICAL PHARMACOLOGY

### 46 Pharmacokinetics

47 Multiple dose ribavirin pharmacokinetic data are available for HCV patients who  
48 received ribavirin in combination with peginterferon alfa-2a. Following administration of  
49 1200 mg/day with food for 12 weeks mean±SD (n=39; body weight >75 kg)  $AUC_{0-12hr}$   
50 was  $25,361 \pm 7110$  ng·hr/mL and  $C_{max}$  was  $2748 \pm 818$  ng/mL. The average time to reach  
51  $C_{max}$  was 2 hours. Trough ribavirin plasma concentrations following 12 weeks of dosing  
52 with food were  $1662 \pm 545$  ng/mL in HCV infected patients who received 800 mg/day  
53 (n=89), and  $2112 \pm 810$  ng/mL in patients who received 1200 mg/day (n=75; body weight  
54 >75 kg).

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

### 60 Effect of Food on Absorption of Ribavirin

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

### 66 Elimination and Metabolism

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

## COPEGUS® (ribavirin, USP)

### 70 **Special Populations**

#### 71 Race

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

#### 75 Renal Dysfunction

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

#### 81 Hepatic Impairment

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

#### 85 Pediatric Patients

86 Pharmacokinetic evaluations in pediatric patients have not been performed.

#### 87 Elderly Patients

88 Pharmacokinetic evaluations in elderly patients have not been performed.

#### 89 Gender

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

### 92 **Drug Interactions**

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

#### 94 Nucleoside Analogues

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

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

#### 105 Drugs Metabolized by Cytochrome P450

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

## COPEGUS® (ribavirin, USP)

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

### 111 **CLINICAL STUDIES**

#### 112 **HCV Patients**

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

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

131 **Table 1 Sustained Virologic Response (SVR) to Combination**  
132 **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%)

133  
134 Difference in overall treatment response (PEGASYS/COPEGUS – Interferon alfa-2b/ribavirin) was 9%  
135 (95% CI 2.3, 15.3).

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

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

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

### 145 HCV Genotypes

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

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

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

155 **Table 2 Sustained Virologic Response as a Function of Genotype**  
156 **(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%)

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

158 \*\*1000 mg for body weight <75 kg; 1200 mg for body weight ≥75 kg.

159

### 160 Other Treatment Response Predictors

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

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

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

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

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

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

189 **Table 3 Sustained Virologic Response in Patients With Chronic**  
190 **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%)

191 \*PEGASYS + COPEGUS vs. PEGASYS; PEGASYS + COPEGUS vs. ROFERON-A + COPEGUS p-  
192 value <0.0001 (Cochran-Mantel-Haenszel).  
193

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

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

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

## COPEGUS® (ribavirin, USP)

### 205 **INDICATIONS AND USAGE**

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

### 213 **CONTRAINDICATIONS**

214 COPEGUS (ribavirin) is contraindicated in:

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

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

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

### 225 **WARNINGS**

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

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

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

### 238 **General**

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

242 **Pregnancy**

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

256 **Anemia**

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

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

276 **Hepatic Failure**

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

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

### 291 **Hypersensitivity**

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

### 302 **Pulmonary**

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

### 309 **Other**

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

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

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

### 317 **PRECAUTIONS**

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

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

## COPEGUS® (ribavirin, USP)

### 327 **Information for Patients**

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

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

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

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

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

352 Patients should be advised to take COPEGUS with food.

### 353 **Laboratory Tests**

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

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

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

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

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

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

### 380 **Drug Interactions**

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

### 383 **Nucleoside Analogues**

#### 384 *NRTIs*

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

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

#### 394 *Didanosine*

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

#### 399 *Zidovudine*

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

## COPEGUS® (ribavirin, USP)

### 404 *Lamivudine, Stavudine, and Zidovudine*

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

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

#### 411 Carcinogenesis

412 In a p53 (+/-) mouse carcinogenicity study and a rat 2-year carcinogenicity study at doses  
413 up to the maximum tolerated doses of 100 mg/kg/day and 60 mg/kg/day, respectively,  
414 ribavirin was not oncogenic. On a body surface area basis, these doses are approximately  
415 0.5 and 0.6 times the maximum recommended human 24-hour dose of ribavirin.

#### 416 Mutagenesis

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

#### 424 Impairment of Fertility

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

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

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

## COPEGUS® (ribavirin, USP)

### 443 **Pregnancy**

#### 444 **Pregnancy: Category X (see CONTRAINDICATIONS)**

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

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

#### 456 *Treatment and Posttreatment: Potential Risk to the Fetus*

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

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

#### 470 *Ribavirin Pregnancy Registry*

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

#### 475 *Animal Toxicology*

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

## COPEGUS® (ribavirin, USP)

### 482 **Nursing Mothers**

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

### 487 **Pediatric Use**

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

### 490 **Geriatric Use**

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

### 498 **Effect of Gender**

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

## 501 **ADVERSE REACTIONS**

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

504 The most common life-threatening or fatal events induced or aggravated by PEGASYS  
505 and COPEGUS were depression, suicide, relapse of drug abuse/overdose, and bacterial  
506 infections, each occurring at a frequency of <1%. Hepatic decompensation occurred in  
507 2% (10/574) of CHC/HIV patients (see **WARNINGS: Hepatic Failure**).

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

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

## COPEGUS® (ribavirin, USP)

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

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

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

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

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

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

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

	CHC Combination Therapy Study NV15801
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**COPEGUS® (ribavirin, USP)**

Body System	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
Back pain	5	5
<b>Neurological</b>		
Headache	43	49

**COPEGUS® (ribavirin, USP)**

<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>
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

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

560 \*\* Severe hematologic abnormalities (lymphocyte <0.5 x 10<sup>9</sup>/L; hemoglobin <10 g/dL; neutrophil <0.75 x  
561 10<sup>9</sup>/L; platelet <50 x 10<sup>9</sup>/L).

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

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

### 568 **Laboratory Test Values**

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

### 574 **Postmarketing Experience**

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

### 580 **OVERDOSAGE**

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

## 586 **DOSAGE AND ADMINISTRATION**

### 587 **CHC Mono-infection**

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

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

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

597

598 **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

599 Genotypes non-1 showed no increased response to treatment beyond 24 weeks (see **Table 2**).

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

601 **CHC with HIV Coinfection**

602 The recommended dose for hepatitis C in HCV/HIV coinfecting patients is PEGASYS  
603 180 µg sc once weekly and COPEGUS 800 mg po daily for a total of 48 weeks,  
604 regardless of genotype.

605 **Dose Modifications**

606 **If severe adverse reactions or laboratory abnormalities develop during combination**  
607 **COPEGUS/PEGASYS therapy, the dose should be modified or discontinued, if**  
608 **appropriate, until the adverse reactions abate. If intolerance persists after dose**  
609 **adjustment, COPEGUS/PEGASYS therapy should be discontinued.**

610 COPEGUS should be administered with caution to patients with pre-existing cardiac  
611 disease (see **Table 6**). Patients should be assessed before commencement of therapy and  
612 should be appropriately monitored during therapy. If there is any deterioration of  
613 cardiovascular status, therapy should be stopped (see **WARNINGS**).

614 **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

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

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

621 **Renal Impairment**

622 COPEGUS should not be used in patients with creatinine clearance <50 mL/min (see  
623 **WARNINGS** and **CLINICAL PHARMACOLOGY: Special Populations**).

## **COPEGUS<sup>®</sup> (ribavirin, USP)**

### **624 HOW SUPPLIED**

625 COPEGUS<sup>®</sup> (ribavirin) is available as tablets for oral administration. Each tablet contains  
626 200 mg of ribavirin and is light pink to pink colored, flat, oval-shaped, film-coated, and  
627 engraved with RIB 200 on one side and ROCHE on the other side. They are packaged as  
628 bottle of 168 tablets (NDC 0004-0086-94).

### **629 Storage Conditions**

630 Store the COPEGUS<sup>®</sup> Tablets bottle at 25°C (77°F); excursions are permitted between  
631 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep bottle  
632 tightly closed.

633 REBETRON<sup>™</sup> is a trademark of Schering Corporation.

634 PI Revised: March 2010

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## MEDICATION GUIDE

637

### COPEGUS®

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### (ribavirin, USP)

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### TABLETS

640

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?**

645

**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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656

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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## COPEGUS® (ribavirin, USP)

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

### 678 **What is COPEGUS?**

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

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

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

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

691 **Do not use COPEGUS if:**

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

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

## COPEGUS® (ribavirin, USP)

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

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### 749 **How should I take COPEGUS?**

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

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

### 772 **What should I avoid while taking COPEGUS?**

#### 773 **Avoid the following during COPEGUS treatment:**

- 774 • **Do not get pregnant.** If you or your sexual partner get pregnant during treatment  
775 with COPEGUS or in the 6 months after treatment ends, tell your healthcare provider  
776 right away. (See **“What is the most important information I should know about**  
777 **COPEGUS?”**.)

778 Talk with your healthcare provider about birth control methods and how to avoid  
779 pregnancy. You must use extreme care to avoid pregnancy during and for 6 months  
780 after treatment in female and male patients.

- 781 • **Do not take COPEGUS alone to treat your hepatitis C virus infection.**  
782 COPEGUS should be used in combination with PEGASYS (peginterferon alfa-2a) to  
783 treat chronic hepatitis C virus infections. (See **“What is the most important**  
784 **information I should know about COPEGUS?”**.)

- 785 • **Do not breast feed.** COPEGUS may pass through your milk and may harm your  
786 baby.

- 787 • **Do not drink alcohol**, including beer, wine, and liquor. This may make your liver  
788 disease worse.

## COPEGUS® (ribavirin, USP)

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

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

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

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

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

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

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

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

809 • trouble breathing

810 • hives or swelling

811 • chest pain

812 • severe stomach pain or low back pain

813 • bloody diarrhea or bloody stools (bowel movements). These may look like black tar.

814 • bruising or unusual bleeding

815 • change in your vision

816 • high fever (temperature greater than 100.5°F)

817 • you have psoriasis (a skin disease) and it gets worse

818 • you become very depressed or think about suicide (ending your life)

819 • Skin rash can occur in patients taking PEGASYS. In some patients a rash can be  
820 serious. If you develop a rash with fever, blisters, or sores in your mouth, nose or  
821 eyes or conjunctivitis (red or inflamed eyes, like “pink eye”), stop using PEGASYS  
822 and call your doctor right away

823

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

826 • feeling tired

827 • nausea and appetite loss

828 • rash and itching

829 • cough

## COPEGUS® (ribavirin, USP)

830 These are not all the possible side effects of COPEGUS treatment. For more information,  
831 ask your doctor or pharmacist and see the PEGASYS Medication Guide. Call your doctor  
832 for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-  
833 1088. You may also report side effects to Roche at 1-800-526-6367.

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

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

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

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

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

846 Please refer to the PEGASYS Medication Guide for storage information about  
847 PEGASYS injection.

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

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

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

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

857 Active Ingredient: ribavirin

858 Inactive Ingredients: The core of the tablet contains corn starch, magnesium stearate,  
859 microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. The  
860 coating of the tablet contains ethyl cellulose (200 mg tablet only), hydroxypropylmethyl  
861 cellulose, red iron oxide, talc, titanium dioxide, triacetin, and yellow iron oxide.  
862

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

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