



## **ROFERON -A**

**(Interferon alfa-2a, recombinant)**

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

Alpha-interferons, including Interferon alfa-2a, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping Interferon alfa-2a therapy (see **WARNINGS** and **ADVERSE REACTIONS**).

## **DESCRIPTION**

Roferon-A (Interferon alfa-2a, recombinant) is a sterile protein product for use by injection. Roferon-A is manufactured by recombinant DNA technology that employs a genetically engineered *Escherichia coli* bacterium containing DNA that codes for the human protein. Interferon alfa-2a, recombinant is a highly purified protein containing 165 amino acids, and it has an approximate molecular weight of 19,000 daltons. Fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride, 5 mg/L. However, the presence of the antibiotic is not detectable in the final product. Roferon-A is supplied in prefilled syringes. Each glass syringe barrel contains 0.5 mL of product. In addition, there is a needle, which is ½ inch in length.

## **Single Use Prefilled Syringes**

*3 million IU (11.1 mcg/0.5 mL) Roferon-A per syringe* — The solution is colorless and each 0.5 mL contains 3 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

*6 million IU (22.2 mcg/0.5 mL) Roferon-A per syringe* — The solution is colorless and each 0.5 mL contains 6 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

*9 million IU (33.3 mcg/0.5 mL) Roferon-A per syringe* — The solution is colorless and each 0.5 mL contains 9 MIU of Interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

34 The route of administration is by subcutaneous injection.

CLINICAL PHARMACOLOGY

36 The mechanism by which Interferon alfa-2a, recombinant, or any other interferon, exerts  
37 antitumor or antiviral activity is not clearly understood. However, it is believed that direct

38 antiproliferative action against tumor cells, inhibition of virus replication and modulation of  
39 the host immune response play important roles in antitumor and antiviral activity.

40 The biological activities of Interferon alfa-2a, recombinant are species-restricted, i.e., they  
41 are expressed in a very limited number of species other than humans. As a consequence,  
42 preclinical evaluation of Interferon alfa-2a, recombinant has involved in vitro experiments  
43 with human cells and some in vivo experiments.<sup>1</sup> Using human cells in culture, Interferon  
44 alfa-2a, recombinant has been shown to have antiproliferative and immunomodulatory  
45 activities that are very similar to those of the mixture of interferon alfa subtypes produced  
46 by human leukocytes. In vivo, Interferon alfa-2a, recombinant has been shown to inhibit  
47 the growth of several human tumors growing in immunocompromised (nude) mice.  
48 Because of its species-restricted activity, it has not been possible to demonstrate antitumor  
49 activity in immunologically intact syngeneic tumor model systems, where effects on the  
50 host immune system would be observable. However, such antitumor activity has been  
51 repeatedly demonstrated with, for example, mouse interferon-alfa in transplantable mouse  
52 tumor systems. The clinical significance of these findings is unknown.

53 The metabolism of Interferon alfa-2a, recombinant is consistent with that of alpha-  
54 interferons in general. Alpha-interferons are totally filtered through the glomeruli and  
55 undergo rapid proteolytic degradation during tubular reabsorption, rendering a negligible  
56 reappearance of intact alfa interferon in the systemic circulation. Small amounts of  
57 radiolabeled Interferon alfa-2a, recombinant appear in the urine of isolated rat kidneys,  
58 suggesting near complete reabsorption of Interferon alfa-2a, recombinant catabolites. Liver  
59 metabolism and subsequent biliary excretion are considered minor pathways of elimination  
60 for alfa interferons.

61 The serum concentrations of Interferon alfa-2a, recombinant reflected a large intersubject  
62 variation in both healthy volunteers and patients with disseminated cancer.

63 In healthy people, Interferon alfa-2a, recombinant exhibited an elimination half-life of 3.7  
64 to 8.5 hours (mean 5.1 hours), volume of distribution at steady-state of 0.223 to 0.748 L/kg  
65 (mean 0.400 L/kg) and a total body clearance of 2.14 to 3.62 mL/min/kg (mean 2.79  
66 mL/min/kg) after a 36 MIU ( $2.2 \times 10^8$  pg) intravenous infusion. After intramuscular and  
67 subcutaneous administrations of 36 MIU, peak serum concentrations ranged from 1500 to  
68 2580 pg/mL (mean 2020 pg/mL) at a mean time to peak of 3.8 hours and from 1250 to  
69 2320 pg/mL (mean 1730 pg/mL) at a mean time to peak of 7.3 hours, respectively. The  
70 apparent fraction of the dose absorbed after intramuscular injection was greater than 80%.

71 The pharmacokinetics of Interferon alfa-2a, recombinant after single intramuscular doses to  
72 patients with disseminated cancer were similar to those found in healthy volunteers. Dose  
73 proportional increases in serum concentrations were observed after single doses up to 198  
74 MIU. There were no changes in the distribution or elimination of Interferon alfa-2a,  
75 recombinant during twice daily (0.5 to 36 MIU), once daily (1 to 54 MIU), or three times  
76 weekly (1 to 136 MIU) dosing regimens up to 28 days of dosing. Multiple intramuscular  
77 doses of Interferon alfa-2a, recombinant resulted in an accumulation of two to four times  
78 the single dose serum concentrations. There is no pharmacokinetic information in patients  
79 with chronic hepatitis C, hairy cell leukemia, and chronic myelogenous leukemia.

80 Serum neutralizing activity, determined by a highly sensitive enzyme immunoassay, and a  
81 neutralization bioassay, was detected in approximately 25% of all patients who received  
82 Roferon-A.<sup>2</sup> Antibodies to human leukocyte interferon may occur spontaneously in certain  
83 clinical conditions (cancer, systemic lupus erythematosus, herpes zoster) in patients who  
84 have never received exogenous interferon.<sup>3</sup> The significance of the appearance of serum  
85 neutralizing activity is not known.

## 86 **Clinical Studies**

87 Studies have shown that Roferon-A can normalize serum ALT, improve liver histology and  
88 reduce viral load in patients with chronic hepatitis C. Other studies have shown that  
89 Roferon-A can produce clinically meaningful tumor regression or disease stabilization in  
90 patients with hairy cell leukemia.<sup>4,5</sup> In Ph-positive Chronic Myelogenous Leukemia,  
91 Roferon-A supplemented with intermittent chemotherapy has been shown to prolong  
92 overall survival and to delay disease progression compared to patients treated with  
93 chemotherapy alone.<sup>6</sup> In addition, Roferon-A has been shown to produce sustained  
94 complete cytogenetic responses in a small subset of patients with CML in chronic phase.  
95 The activity of Roferon-A in Ph-negative CML has not been determined.

## 96 **Effects On Chronic Hepatitis C**

97 The safety and efficacy of Roferon-A was evaluated in multiple clinical trials involving  
98 over 2000 patients 18 years of age or older with hepatitis, with or without cirrhosis, who  
99 had elevated serum alanine aminotransferase (ALT) levels and tested positive for antibody  
100 to hepatitis C. Roferon-A was given three times a week (tiw) by subcutaneous (SC) or  
101 intramuscular (IM) injection in a variety of dosing regimens, including dose escalation and  
102 de-escalation regimens. Normalization of serum ALT was defined in all studies as two  
103 consecutive normal serum ALT values at least 21 days apart. A sustained response (SR)  
104 was defined as normalization of ALT both at the end of treatment and at the end of at least  
105 6 months of treatment-free follow-up.

106 In trials in which Roferon-A was administered for 6 months, 6 MIU, 3 MIU, and 1 MIU  
107 were directly compared. Six MIU was associated with higher SR rates but greater toxicity  
108 (see **ADVERSE REACTIONS**). In studies in which the same dose of Roferon-A was  
109 administered for 6 or 12 months, the longer duration was associated with higher SR rates  
110 and adverse events were no more severe or frequent in the second 6 months than in the first  
111 6 months. Based on these data, the recommended regimens are 3 MIU for 12 months or 6  
112 MIU for the first 3 months followed by 3 MIU for the next 9 months (see Table 1 and  
113 **DOSAGE AND ADMINISTRATION**). There are no direct comparisons of these two  
114 regimens.

115 Younger patients (e.g., less than 35 years of age) and patients without cirrhosis on liver  
116 biopsy were more likely to respond completely to Roferon-A than those patients greater  
117 than 35 years of age or patients with cirrhosis on liver biopsy.

118 In the two studies in which Roferon-A was administered subcutaneously three times  
119 weekly for 12 months, 20/173 (12%) patients experienced a sustained response to therapy  
120 (see Table 1). Of these patients, 15/173 (9%) maintained this sustained response during  
121 continuous follow-up for up to four years. Patients who have ALT normalization but who

122 fail to have a sustained response following an initial course of therapy may benefit from  
123 retreatment with higher doses of Roferon-A (see **DOSAGE AND ADMINISTRATION**).

124 A subset of patients had liver biopsies performed both before and after treatment with  
125 Roferon-A. An improvement in liver histology as assessed by Knodell Histology Activity  
126 Index was generally observed.

127 A retrospective subgroup analysis of 317 patients from two studies suggested a correlation  
128 between improvement in liver histology, durable serum ALT response rates, and decreased  
129 viral load as measured by the polymerase chain reaction (PCR).

130 **Table 1 ALT Normalization in Patients Receiving Therapy With**  
131 **Roferon-A for 12 Months**

Study No.	Dose (MIU)	N	End of Treatment [% (95% CI)]	End of Observation (Sustained Response SR) [% (95% CI)] *
1**	3	56	23	11
2	3	117	23	12
1 and 2 Combined	3	173	23 (17-30)	12 (7-17)
3	6-3	210	25 (19-31)	19 (14-25)

132 \* All patients were followed for 6 months after end of treatment.

133 \*\* EOT and SR rates for Placebo (study 1) were 0.

#### 134 **Effects on Ph-Positive Chronic Myelogenous Leukemia (CML)**

135 Roferon-A was evaluated in two trials of patients with chronic phase CML. Study DM84-  
136 38 was a single center phase II study conducted at the MD Anderson Cancer Center, which  
137 enrolled 91 patients, 81% were previously treated, 82% were Ph positive, and 63%  
138 received Roferon-A within 1 year of diagnosis. Study MI400 was a multicenter randomized  
139 phase III study conducted in Italy by the Italian Cooperative Study Group on CML in 335  
140 patients; 226 Roferon-A and 109 chemotherapy. Patients with Ph-positive, newly  
141 diagnosed or minimally treated CML were randomized (ratio 2:1) to either Roferon-A or  
142 conventional chemotherapy with either hydroxyurea or busulfan. In study DM84-38,  
143 patients started Roferon-A at 9 MIU/day, whereas in study MI400, it was progressively  
144 escalated from 3 to 9 MIU/day over the first month. In both trials, dose escalation for  
145 insufficient hematologic response, and dose attenuation or interruption for toxicity was  
146 permitted. No formal guidelines for dose attenuation were given in the chemotherapy arm  
147 of study MI400. In addition, in the Roferon-A arm, the MI400 protocol allowed the  
148 addition of intermittent single agent chemotherapy for insufficient hematologic response to  
149 Roferon-A alone. In this trial, 44% of the Roferon-A treated patients also received  
150 intermittent single agent chemotherapy at some time during the study.

151 The two studies were analyzed according to uniform response criteria. For hematologic  
152 response: complete response (WBC <9x10<sup>9</sup>/L, normalization of the differential with no

153 immature forms in the peripheral blood, disappearance of splenomegaly), partial response  
154 (>50% decrease from baseline of WBC to <20% $\times 10^9$ /L). For cytogenetic response:  
155 complete response (0% Ph-positive metaphases), partial response (1% to 34% Ph-positive  
156 metaphases).

157 In study DM84-38, the median survival from initiation of Roferon-A was 47 months. In  
158 study MI400, the median survival for the patients on the interferon arm was 69 months,  
159 which was significantly better than the 55 months seen in the chemotherapy control group  
160 (48 patients in study MI400 proceeded to BMT and in study DM84-38, 15 patients  
161 proceeded to BMT). Roferon-A treatment significantly delayed disease progression to  
162 blastic phase as evidenced by a median time to disease progression of 69 months to 46  
163 months with chemotherapy.

164 By multivariate analysis of prognostic factors associated with all 335 patients entered into  
165 the randomized study, treatment with Roferon-A (with or without intermittent additional  
166 chemotherapy; p=0.006), Sokal index<sup>7</sup> (p=0.006) and WBC (p=0.023) were the three  
167 variables associated with an improved survival, independent of other baseline  
168 characteristics (Karnofsky performance status and hemoglobin being the other factors  
169 entered into the model).

170 In study MI400, overall hematologic responses, [complete responses (CR) and partial  
171 responses (PR)], were observed in approximately 60% of patients treated with Roferon-A  
172 (40% CR, 20% PR), compared to 70% with chemotherapy (30% CR, 40% PR). The  
173 median time to reach a complete hematologic response was 5 months in the Roferon-A arm  
174 and 4 months in the chemotherapy arm. The overall cytogenetic response rate (CR+PR), in  
175 patients receiving Roferon-A, was 10% and 12% in studies MI400 and DM84-38,  
176 respectively, according to the intent-to-treat principle. In contrast, only 2% of the patients  
177 in the chemotherapy arm of study MI400 achieved a cytogenetic response (with no  
178 complete responses). Cytogenetic responses were observed only in patients who had  
179 complete hematologic responses. In study DM84-38, hematologic and cytogenetic response  
180 rates were higher in the subset of patients treated with Roferon-A within 1 year of  
181 diagnosis (76% and 17%, respectively) compared to the subset initiating Roferon-A  
182 therapy more than 1 year from diagnosis (29% and 4%, respectively). In an exploratory  
183 analysis, patients who achieved a cytogenetic response lived longer than those who did not.

184 Severe adverse events were observed in 66% and 31% of patients on study DM84-38 and  
185 MI400, respectively. Dose reduction and temporary cessation of therapy was required  
186 frequently. Permanent cessation of Roferon-A, due to intolerable side effects, was required  
187 in 15% and 23% of patients on studies DM84-38 and MI400, respectively (see **ADVERSE  
188 REACTIONS**).

189 Limited data are available on the use of Roferon-A in children with Ph-positive, adult-type  
190 CML. A published report on 15 children with CML suggests a safety profile similar to that  
191 seen in adult CML; clinical responses were also observed<sup>8</sup> (see **DOSAGE AND  
192 ADMINISTRATION**).

193 **Effects on Hairy Cell Leukemia**

194 A multicenter US phase II study (N2752) enrolled 218 patients; 75 were evaluable for  
195 efficacy in a preliminary analysis; 218 patients were evaluable for safety. Patients were to  
196 receive a starting dose of Roferon-A up to 6 MIU/m<sup>2</sup>/day, for an induction period of 4 to 6  
197 months. Responding patients were to receive 12 months maintenance therapy.

198 During the first 1 to 2 months of treatment of patients with hairy cell leukemia, significant  
199 depression of hematopoiesis was likely to occur. Subsequently, there was improvement in  
200 circulating blood cell counts. Of the 75 patients who were evaluable for efficacy following  
201 at least 16 weeks of therapy, 46 (61%) achieved complete or partial response. Twenty-one  
202 patients (28%) had a minor remission, 8 (11%) remained stable, and none had worsening of  
203 disease. All patients who achieved either a complete or partial response had complete or  
204 partial normalization of all peripheral blood elements including hemoglobin level, white  
205 blood cell, neutrophil, monocyte and platelet counts with a concomitant decrease in  
206 peripheral blood and bone marrow hairy cells. Responding patients also exhibited a marked  
207 reduction in red blood cell and platelet transfusion requirements, a decrease in infectious  
208 episodes and improvement in performance status. The probability of survival for 2 years in  
209 patients receiving Roferon-A (94%) was statistically increased compared to a historical  
210 control group (75%).

211 **INDICATIONS AND USAGE**

212 Roferon-A is indicated for the treatment of chronic hepatitis C and hairy cell leukemia in  
213 patients 18 years of age or older. In addition, it is indicated for chronic phase, Philadelphia  
214 chromosome (Ph) positive chronic myelogenous leukemia (CML) patients who are  
215 minimally pretreated (within 1 year of diagnosis).

216 **For Patients With Chronic Hepatitis C**

217 Roferon-A is indicated for use in patients with chronic hepatitis C diagnosed by HCV  
218 antibody and/or a history of exposure to hepatitis C who have compensated liver disease  
219 and are 18 years of age or older. A liver biopsy and a serum test for the presence of  
220 antibody to HCV should be performed to establish the diagnosis of chronic hepatitis C.  
221 Other causes of hepatitis, including hepatitis B, should be excluded prior to therapy with  
222 Roferon-A.

223 **CONTRAINDICATIONS**

224 Roferon-A is contraindicated in patients with:

- 225 • Hypersensitivity to Roferon-A or any of its components  
226 • Autoimmune hepatitis  
227 • Hepatic decompensation (Child-Pugh class B and C) before or during treatment

228 Roferon-A is contraindicated in neonates and infants because it contains benzyl alcohol.  
229 Benzyl alcohol is associated with an increased incidence of neurologic and other  
230 complications in neonates and infants, which are sometimes fatal.

231 **WARNINGS**

232 Roferon-A should be administered under the guidance of a qualified physician (see  
233 **DOSAGE AND ADMINISTRATION**). Appropriate management of the therapy and its  
234 complications is possible only when adequate facilities are readily available.

235 **Neuropsychiatric Disorders**

236 DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL IDEATION,  
237 SUICIDAL ATTEMPTS AND SUICIDES HAVE BEEN REPORTED IN  
238 ASSOCIATION WITH TREATMENT WITH ALFA INTERFERONS, INCLUDING  
239 ROFERON-A, IN PATIENTS WITH AND WITHOUT PREVIOUS PSYCHIATRIC  
240 ILLNESS. Roferon-A should be used with extreme caution in patients who report a history  
241 of depression. Patients should be informed that depression and suicidal ideation may be  
242 side effects of treatment and should be advised to report these side effects immediately to  
243 the prescribing physician. Patients receiving Roferon-A therapy should receive close  
244 monitoring for the occurrence of depressive symptomatology. Psychiatric intervention  
245 and/or cessation of treatment should be considered for patients experiencing depression.  
246 Although dose reduction or treatment cessation may lead to resolution of the depressive  
247 symptomatology, depression may persist and suicides have occurred after withdrawing  
248 therapy (see **PRECAUTIONS** and **ADVERSE REACTIONS**).

249 Central nervous system adverse reactions have been reported in a number of patients.  
250 These reactions included decreased mental status, dizziness, impaired memory, agitation,  
251 manic behavior and psychotic reactions. More severe obtundation and coma have been  
252 rarely observed. Most of these abnormalities were mild and reversible within a few days to  
253 3 weeks upon dose reduction or discontinuation of Roferon-A therapy. Careful periodic  
254 neuropsychiatric monitoring of all patients is recommended. Roferon-A should be used  
255 with caution in patients with seizure disorders and/or compromised central nervous system  
256 function.

257 **Cardiovascular Disorders**

258 Roferon-A should be administered with caution to patients with cardiac disease or with any  
259 history of cardiac illness. Acute, self-limited toxicities (i.e., fever, chills) frequently  
260 associated with Roferon-A administration may exacerbate preexisting cardiac conditions.  
261 Rarely, myocardial infarction has occurred in patients receiving Roferon-A. Cases of  
262 cardiomyopathy have been observed on rare occasions in patients treated with alpha  
263 interferons.

264 **Cerebrovascular Disorders**

265 Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated  
266 with interferon alfa-based therapies, including Roferon-A. Events occurred in patients  
267 with few or no reported risk factors for stroke, including patients less than 45 years of  
268 age. Because these are spontaneous reports, estimates of frequency cannot be made and a  
269 causal relationship between interferon alfa-based therapies and these events is difficult to  
270 establish.

271 **Hypersensitivity**

272 Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction  
273 and anaphylaxis), as well as skin rashes have been rarely observed during alpha-  
274 interferon therapy, including interferon alfa-2a. If a serious reaction develops during  
275 treatment with Roferon-A, discontinue treatment and institute appropriate medical  
276 therapy immediately. Transient rashes do not necessitate interruption of treatment.

277 **Hepatic Disorders**

278 In chronic hepatitis C, initiation of alfa-interferon therapy, including Roferon-A, has been  
279 reported to cause transient liver abnormalities, which in patients with poorly compensated  
280 liver disease can result in increased ascites, hepatic failure or death.

281 **Gastrointestinal Disorders**

282 Infrequently, severe or fatal gastrointestinal hemorrhage has been reported in association  
283 with alpha-interferon therapy.

284 Ulcerative, and hemorrhagic/ischemic colitis, sometimes fatal, have been observed within  
285 12 weeks of starting alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever  
286 are the typical manifestations of colitis. Roferon-A should be discontinued immediately if  
287 these symptoms develop. The colitis usually resolves within 1 to 3 weeks of  
288 discontinuation of alpha interferon.

289 **Infections**

290 While fever may be associated with the flu-like syndrome reported commonly during  
291 interferon therapy, other causes of high or persistent fever must be ruled out, particularly  
292 in patients with neutropenia. Serious and severe infections (bacterial, viral, fungal), some  
293 fatal, have been reported during treatment with alpha interferons including Roferon-A.  
294 Appropriate anti-infective therapy should be started immediately and discontinuation of  
295 therapy should be considered.

296 **Bone Marrow Toxicity**

297 Alpha-interferons suppress bone marrow function and may result in severe cytopenias  
298 and anemia including very rare events of aplastic anemia. Cytopenias (e.g., leukopenia,  
299 thrombocytopenia) can lead to an increased risk of infections or hemorrhage. It is advised  
300 that complete blood counts (CBC) be obtained pretreatment and monitored routinely  
301 during therapy. Alpha interferon therapy should be discontinued in patients who develop  
302 severe decreases in neutrophil ( $<0.5 \times 10^9/L$ ) or platelet counts ( $<25 \times 10^9/L$ ).

303 Caution should be exercised when administering Roferon-A to patients with  
304 myelosuppression or when Roferon-A is used in combination with other agents that are  
305 known to cause myelosuppression. Synergistic toxicity has been observed when Roferon-A  
306 is administered in combination with zidovudine (AZT).<sup>9</sup>

307 **Endocrine Disorders**

308 Roferon-A causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia has  
309 been observed in patients treated with Roferon-A. Symptomatic patients should have their  
310 blood glucose measured and followed-up accordingly. Patients with diabetes mellitus may  
311 require adjustment of their anti-diabetic regimen.

312 **Pulmonary Disorders**

313 Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial  
314 pneumonitis and sarcoidosis, some resulting in respiratory failure and/or patient deaths,  
315 may be induced or aggravated by alpha interferon therapy. Patients who develop persistent  
316 or unexplained pulmonary infiltrates or pulmonary function impairment should discontinue  
317 treatment with Roferon-A.

318 **Ophthalmologic Disorders**

319 Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein  
320 thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema  
321 are induced or aggravated by treatment with Interferon alfa-2a or other alpha interferons.  
322 All patients should receive an eye examination at baseline. Patients with preexisting  
323 ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive  
324 periodic ophthalmologic exams during interferon alpha treatment. Any patient who  
325 develops ocular symptoms should receive a prompt and complete eye examination.  
326 Interferon alfa-2a treatment should be discontinued in patients who develop new or  
327 worsening ophthalmologic disorders.

328 **Pancreatitis**

329 Pancreatitis has been observed in patients receiving alpha interferon treatment, including  
330 those who developed marked triglyceride elevations. In some cases, fatalities have been  
331 observed. Although a causal relationship to Roferon-A has not been established, marked  
332 triglyceride elevation is a risk factor for development of pancreatitis. Roferon-A should  
333 be suspended if symptoms or signs suggestive of pancreatitis are observed. In patients  
334 diagnosed with pancreatitis, discontinuation of therapy with Roferon-A should be  
335 considered.

336 **PRECAUTIONS**

337 **General**

338 In all instances where the use of Roferon-A is considered for chemotherapy, the physician  
339 must evaluate the need and usefulness of the drug against the risk of adverse reactions.  
340 Most adverse reactions are reversible if detected early. If severe reactions occur, the drug  
341 should be reduced in dosage or discontinued and appropriate corrective measures should be  
342 taken according to the clinical judgment of the physician. Reinstitution of Roferon-A  
343 therapy should be carried out with caution and with adequate consideration of the further  
344 need for the drug and, alertness to possible recurrence of toxicity. The minimum effective  
345 doses of Roferon-A for treatment of hairy cell leukemia and chronic myelogenous  
346 leukemia have not been established.

347 Variations in dosage and adverse reactions exist among different brands of Interferon.  
348 Therefore, do not use different brands of Interferon in a single treatment regimen.

349 The safety and efficacy of Roferon-A have not been established in organ transplant  
350 recipients.

### 351 **Renal Impairment**

352 Dose-limiting renal toxicities were unusual. Infrequently, severe renal toxicities,  
353 sometimes requiring renal dialysis, have been reported with alpha-interferon therapy  
354 alone or in combination with IL-2. In patients with impaired renal function, signs and  
355 symptoms of interferon toxicity should be closely monitored. Roferon-A should be used  
356 with caution in patients with creatinine clearance <50 mL/min.

### 357 **Autoimmune Disease**

358 Development or exacerbation of autoimmune diseases including idiopathic  
359 thrombocytopenic purpura, vasculitis, Raynaud's phenomenon, rheumatoid arthritis,  
360 psoriasis, interstitial nephritis, thyroiditis, lupus erythematosus, hepatitis, myositis and  
361 rhabdomyolysis have been observed in patients treated with alpha-interferons. Any  
362 patient developing an autoimmune disorder during treatment should be closely monitored  
363 and, if appropriate, treatment should be discontinued.

### 364 **Information for Patients**

365 Patients should be cautioned not to change brands of Interferon without medical  
366 consultation, as a change in dosage may result. Patients should be informed regarding the  
367 potential benefits and risks attendant to the use of Roferon-A. If home use is determined to  
368 be desirable by the physician, instructions on appropriate use should be given, including  
369 review of the contents of the enclosed Medication Guide. Patients should be well hydrated,  
370 especially during the initial stages of treatment.

371 Patients should be thoroughly instructed in the importance of proper disposal procedures  
372 and cautioned against reusing syringes and needles. If home use is prescribed, a puncture-  
373 resistant container for the disposal of used syringes and needles should be supplied to the  
374 patient. The full container should be disposed of according to directions provided by the  
375 physician (see **Medication Guide**).

376 Patients should be advised that laboratory evaluations are required before starting therapy  
377 and periodically thereafter (see **Laboratory Tests**).

378 Patients receiving high-dose alpha-interferon should be cautioned against performing tasks  
379 that require complete mental alertness such as operating machinery or driving a motor  
380 vehicle. Patients to be treated with Roferon-A should be informed that depression and  
381 suicidal ideation may be side effects of treatment and should be advised to report these side  
382 effects immediately to the prescribing physician.

383    **Laboratory Tests**

384    Leukopenia and elevation of hepatic enzymes occurred frequently but were rarely dose-  
385    limiting. Thrombocytopenia occurred less frequently. Proteinuria and increased cells in  
386    urinary sediment were also seen infrequently.

387    Complete blood counts with differential platelet counts and clinical chemistry tests should  
388    be performed before initiation of Roferon-A therapy and at appropriate periods during  
389    therapy. Patients with neutrophil count <1500/mm<sup>3</sup>, platelet count <75,000/mm<sup>3</sup>,  
390    hemoglobin <10 g/dL and creatinine >1.5 mg/dL were excluded from several major  
391    chronic hepatitis C studies; patients with these laboratory abnormalities should be carefully  
392    monitored if treated with Roferon-A. Since responses of hairy cell leukemia, chronic  
393    hepatitis C and chronic myelogenous leukemia are not generally observed for 1 to 3 months  
394    after initiation of treatment, very careful monitoring for severe depression of blood cell  
395    counts is warranted during the initial phase of treatment.

396    Those patients who have preexisting cardiac abnormalities and/or are in advanced stages of  
397    cancer should have electrocardiograms taken before and during the course of treatment.

398    **Liver Function.** For patients being treated for chronic hepatitis C, serum ALT should be  
399    evaluated before therapy to establish baselines and repeated at week 2 and monthly  
400    thereafter following initiation of therapy for monitoring clinical response. Patients  
401    developing liver function abnormalities during Roferon-A treatment should be closely  
402    monitored and if necessary treatment should be discontinued. Use of alpha-interferons has  
403    been rarely associated with severe hepatic dysfunction and liver failure.

404    **Thyroid Function.** Patients with preexisting thyroid abnormalities may be treated if  
405    normal thyroid stimulating hormone (TSH) levels can be maintained by medication.  
406    Testing of TSH levels in these patients is recommended at baseline and every 3 months  
407    following initiation of therapy.

408    **Triglycerides.** Elevated triglyceride levels have been observed in patients treated with  
409    interferons including Roferon-A therapy. Triglyceride levels should be monitored  
410    periodically during treatment and elevated levels should be managed as clinically  
411    appropriate. Hypertriglyceridemia may result in pancreatitis. Discontinuation of Roferon-A  
412    therapy should be considered for patients with persistently elevated triglycerides (e.g.,  
413    triglycerides >1000 mg/dL) associated with symptoms of potential pancreatitis, such as  
414    abdominal pain, nausea, or vomiting.

415    **Drug Interactions**

416    Roferon-A has been reported to reduce the clearance of theophylline.<sup>10,11</sup> The clinical  
417    relevance of this interaction is presently unknown. Caution should be exercised when  
418    administering Roferon-A in combination with other potentially myelosuppressive agents.  
419    Synergistic toxicity has been observed when Roferon-A is administered in combination  
420    with zidovudine (AZT) (see **WARNINGS: Bone Marrow Toxicity**).

421    In transplant recipients, therapeutic immunosuppression may be weakened because  
422    interferons also exert an immunostimulatory action.

423 Alpha-interferons may affect the oxidative metabolic process by reducing the activity of  
424 hepatic microsomal cytochrome enzymes in the P450 group. Although the clinical  
425 relevance is still unclear, this should be taken into account when prescribing concomitant  
426 therapy with drugs metabolized by this route.

427 The neurotoxic, hematotoxic or cardiotoxic effects of previously or concurrently  
428 administered drugs may be increased by interferons. Interactions could occur following  
429 concurrent administration of centrally acting drugs. Use of Roferon-A in conjunction with  
430 interleukin-2 may potentiate risks of renal failure.

431 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

432 ***Carcinogenesis***

433 Roferon-A has not been tested for its carcinogenic potential.

434 ***Mutagenesis***

435 A. Internal Studies — Ames tests using six different tester strains, with and without  
436 metabolic activation, were performed with Roferon-A up to a concentration of 1920  
437 µg/plate. There was no evidence of mutagenicity.

438 Human lymphocyte cultures were treated in vitro with Roferon-A at noncytotoxic  
439 concentrations. No increase in the incidence of chromosomal damage was noted.

440 B. Published Studies — There are no published studies on the mutagenic potential of  
441 Roferon-A. However, a number of studies on the genotoxicity of human leukocyte  
442 interferon have been reported.

443 A chromosomal defect following the addition of human leukocyte interferon to lymphocyte  
444 cultures from a patient suffering from a lymphoproliferative disorder has been reported.

445 In contrast, other studies have failed to detect chromosomal abnormalities following  
446 treatment of lymphocyte cultures from healthy volunteers with human leukocyte interferon.

447 It has also been shown that human leukocyte interferon protects primary chick embryo  
448 fibroblasts from chromosomal aberrations produced by gamma rays.

449 ***Impairment of Fertility***

450 Roferon-A has been studied for its effect on fertility in Macaca mulatta (rhesus monkeys).  
451 Nonpregnant rhesus females treated with Roferon-A at doses of 5 and 25 MIU/kg/day have  
452 shown menstrual cycle irregularities, including prolonged or shortened menstrual periods  
453 and erratic bleeding; these cycles were considered to be anovulatory on the basis that  
454 reduced progesterone levels were noted and that expected increases in preovulatory  
455 estrogen and luteinizing hormones were not observed. These monkeys returned to a normal  
456 menstrual rhythm following discontinuation of treatment.

457 **Pregnancy**

458 **Pregnancy Category C**

459 Roferon-A has been associated with statistically significant, dose-related increases in  
460 abortions in pregnant rhesus monkeys treated with 1, 5, or 25 MIU/kg/day (approximately  
461 20 to 500 times the human weekly dose, when scaled by body surface area) during the early  
462 to midfetal period of organogenesis (gestation day 22 to 70). Abortifacient activity was also  
463 observed in 2/6 pregnant rhesus monkeys treated with 25 MIU/kg/day Roferon-A (500  
464 times the human dose) during the period of late fetal development (days 79 to 100 of  
465 gestation). No teratogenic effects were seen in either study. However, the validity of  
466 extrapolating doses used in animal studies to human doses is not established. Therefore, no  
467 direct comparison of the doses that induced fetal death in monkeys to dose levels of  
468 Roferon-A used clinically can be made. There are no adequate and well-controlled studies  
469 of Roferon-A in pregnant women. Roferon-A is to be used during pregnancy only if the  
470 potential benefit to the woman justifies the potential risk to the fetus. Roferon-A is  
471 recommended for use in women of childbearing potential and in men only when they are  
472 using effective contraception during therapy.

473 The injectable solution contains benzyl alcohol. The excipient benzyl alcohol can be  
474 transmitted via the placenta. The possibility of toxicity should be taken into account in  
475 premature infants after the administration of Roferon-A solution for injection immediately  
476 prior to birth or Cesarean section.

477 Male fertility and teratologic evaluations have yielded no significant adverse effects to date.

478 **Nursing Mothers**

479 It is not known whether this drug is excreted in human milk. Because many drugs are  
480 excreted in human milk and because of the potential for serious adverse reactions in  
481 nursing infants from Roferon-A, a decision should be made whether to discontinue nursing  
482 or to discontinue the drug, taking into account the importance of the drug to the mother.

483 **Pediatric Use**

484 Use of Roferon-A in children with Ph-positive adult-type CML is supported by evidence  
485 from adequate and well-controlled studies of Roferon-A in adults with additional data from  
486 the literature on the use of alfa interferon in children with CML. A published report on 15  
487 children with Ph-positive adult-type CML suggests a safety profile similar to that seen in  
488 adult CML; clinical responses were also observed<sup>8</sup> (see **DOSAGE AND**  
489 **ADMINISTRATION**).

490 For all other indications, safety and effectiveness have not been established in patients  
491 below the age of 18 years.

492 The injectable solutions are not indicated for use in neonates or infants and should not be  
493 used by patients in that age group. There have been rare reports of death in neonates and  
494 infants associated with excessive exposure to benzyl alcohol (see  
495 **CONTRAINDICATIONS**).

496 **Geriatric Use**

497 In clinical studies of Roferon-A in chronic hepatitis C, 101 patients were 65 years old or  
498 older. The numbers were insufficient to determine if antiviral responses differ from  
499 younger subjects. There were greater proportions of geriatric patients with serious  
500 adverse reactions (9% vs. 6%), withdrawals due to adverse reactions (11% vs. 6%), and  
501 WHO grade III neutropenia and thrombocytopenia.

502 Clinical studies of Roferon-A in chronic myelogenous leukemia or hairy cell leukemia  
503 did not include sufficient numbers of subjects aged 65 or older to determine whether they  
504 respond differently from younger subjects.

505 This drug is known to be excreted by the kidney, and the risk of toxic reactions to this  
506 drug may be greater in patients with impaired renal function. Because elderly patients are  
507 more likely to have decreased renal function, these patients should receive careful  
508 monitoring, including renal function.

509 **ADVERSE REACTIONS**

510 Depressive illness and suicidal behavior, including suicidal ideation, suicide attempt, and  
511 suicides, have been reported in association with the use of alfa-interferon products. The  
512 incidence of reported depression has varied substantially among trials, possibly related to  
513 the underlying disease, dose, duration of therapy and degree of monitoring, but has been  
514 reported to be 15% or higher (see **WARNINGS**).

515 **For Patients With Chronic Hepatitis C**

516 The most frequent adverse experiences were reported to be possibly or probably related to  
517 therapy with 3 MIU tiw Roferon-A, were mostly mild to moderate in severity and  
518 manageable without the need for discontinuation of therapy. A relative increase in the  
519 incidence, severity and seriousness of adverse events was observed in patients receiving  
520 doses above 3 MIU tiw.

521 Adverse reactions associated with the 3 MIU dose include:

522 Flu-like Symptoms: Fatigue (58%), myalgia/arthralgia (51%), flu-like symptoms (33%),  
523 fever (28%), chills (23%), asthenia (6%), sweating (5%), leg cramps (3%) and malaise  
524 (1%).

525 Central and Peripheral Nervous System: Headache (52%), dizziness (13%), paresthesia  
526 (7%), confusion (7%), concentration impaired (4%) and change in taste or smell (3%).

527 Gastrointestinal: Nausea/vomiting (33%), diarrhea (20%), anorexia (14%), abdominal pain  
528 (12%), flatulence (3%), liver pain (3%), digestion impaired (2%) and gingival bleeding  
529 (2%).

530 Psychiatric: Depression (16%), irritability (15%), insomnia (14%), anxiety (5%) and  
531 behavior disturbances (3%).

532 Pulmonary and Cardiovascular: Dryness or inflammation of oropharynx (6%), epistaxis  
533 (4%), rhinitis (3%), arrhythmia (1%) and sinusitis (<1%).

534 Skin: Injection site reaction (29%), partial alopecia (19%), rash (8%), dry skin or pruritus  
535 (7%), hematoma (1%), psoriasis (<1%), cutaneous eruptions (<1%), eczema (<1%) and  
536 seborrhea (<1%).

537 Other: Conjunctivitis (4%), menstrual irregularity (2%) and visual acuity decreased (<1%).

538 Patients receiving 6 MIU tiw experienced a higher incidence of severe psychiatric events  
539 (9%) than those receiving 3 MIU tiw (6%) in two large US studies. In addition, more  
540 patients withdrew from these studies when receiving 6 MIU tiw (11%) than when receiving  
541 3 MIU tiw (7%). Up to half of patients receiving 3 MIU or 6 MIU tiw withdrawing from  
542 the study experienced depression or other psychiatric adverse events. At higher doses  
543 anxiety, sleep disorders, and irritability were observed more frequently. An increased  
544 incidence of fatigue, myalgia/arthralgia, headache, fever, chills, alopecia, sleep  
545 disturbances and dry skin or pruritus was also generally observed during treatment with  
546 higher doses of Roferon-A.

547 Generally there were fewer adverse events reported in the second 6 months of treatment  
548 than in the first 6 months for patients treated with 3 MIU tiw. Patients tolerant of initial  
549 therapy with Roferon-A generally tolerate re-treatment at the same dose, but tend to  
550 experience more adverse reactions at higher doses.

551 Infrequent adverse events (>1% but <3% incidence) included: cold feeling, cough, muscle  
552 cramps, diaphoresis, dyspnea, eye pain, reactivation of herpes simplex, lethargy, edema,  
553 sexual dysfunction, shaking, skin lesions, stomatitis, tooth disorder, urinary tract infection,  
554 weakness in extremities.

555 Triglyceride levels were not evaluated in the clinical trials. However, hypertriglyceridemia  
556 has been reported postmarketing in patients receiving Roferon-A therapy for chronic  
557 hepatitis C.

### 558 **For Patients With Chronic Myelogenous Leukemia**

559 For patients with chronic myelogenous leukemia, the percentage of adverse events, whether  
560 related to drug therapy or not, experienced by patients treated with rIFN $\alpha$ -2a is given  
561 below. Severe adverse events were observed in 66% and 31% of patients on study DM84-  
562 38 and MI400, respectively. Dose reduction and temporary cessation of therapy were  
563 required frequently. Permanent cessation of Roferon-A, due to intolerable side effects, was  
564 required in 15% and 23% of patients on studies DM84-38 and MI400, respectively.

565 Flu-like Symptoms: Fever (92%), asthenia or fatigue (88%), myalgia (68%), chills (63%),  
566 arthralgia/bone pain (47%) and headache (44%).

567 Gastrointestinal: Anorexia (48%), nausea/vomiting (37%) and diarrhea (37%).

568 Central and Peripheral Nervous System: Headache (44%), depression (28%), decreased  
569 mental status (16%), dizziness (11%), sleep disturbances (11%), paresthesia (8%),  
570 involuntary movements (7%) and visual disturbance (6%).

571 Pulmonary and Cardiovascular: Coughing (19%), dyspnea (8%) and dysrhythmia (7%).

572 Skin: Hair changes (including alopecia) (18%), skin rash (18%), sweating (15%), dry skin  
573 (7%) and pruritus (7%).

574 Uncommon adverse events (<4%) reported in clinical studies included chest pain, syncope,  
575 hypotension, impotence, alterations in taste or hearing, confusion, seizures, memory loss,  
576 disturbances of libido, bruising and coagulopathy. Miscellaneous adverse events that were  
577 rarely observed included Coombs' positive hemolytic anemia, aplastic anemia,  
578 hypothyroidism, cardiomyopathy, hypertriglyceridemia and bronchospasm.

### 579 **For Patients With Hairy Cell Leukemia**

580 Constitutional (100%): Fever (92%), fatigue (86%), headache (64%), chills (64%), weight  
581 loss (33%), dizziness (21%) and flu-like symptoms (16%).

582 Integumentary (79%): Skin rash (44%), diaphoresis (22%), partial alopecia (17%), dry skin  
583 (17%) and pruritus (13%).

584 Musculoskeletal (73%): Myalgia (71%), joint or bone pain (25%) and arthritis or  
585 polyarthritis (5%).

586 Gastrointestinal (69%): Anorexia (43%), nausea/vomiting (39%) and diarrhea (34%).

587 Head and Neck (45%): Throat irritation (21%), rhinorrhea (12%) and sinusitis (11%).

588 Pulmonary (40%): Coughing (16%), dyspnea (12%) and pneumonia (11%).

589 Central Nervous System (39%): Dizziness (21%), depression (16%), sleep disturbance  
590 (10%), decreased mental status (10%), anxiety (6%), lethargy (6%), visual disturbance  
591 (6%) and confusion (5%).

592 Cardiovascular (39%): Chest pain (11%), edema (11%) and hypertension (11%).

593 Pain (34%): Pain (24%) and pain in back (16%).

594 Peripheral Nervous System (23%): Paresthesia (12%) and numbness (12%).

595 Rarely (<5%), central nervous system effects including gait disturbance, nervousness,  
596 syncope and vertigo, as well as cardiac adverse events including murmur, thrombophlebitis  
597 and hypotension were reported. Adverse experiences that occurred rarely, and may have  
598 been related to underlying disease, included ecchymosis, epistaxis, bleeding gums and  
599 petechiae. Urticaria and inflammation at the site of injection were also rarely observed.

### 600 **In Other Investigational Studies of Roferon-A**

601 The following infrequent adverse events have been reported with the investigational use  
602 of Roferon-A.

603 Gastrointestinal: Pancreatitis, colitis, gastrointestinal hemorrhage, stomatitis (<5%);  
604 constipation (<3%); hepatitis, abdominal fullness, hypermotility, excessive salivation,  
605 gastric distress (<1%).

606 Cardiovascular: Palpitations (<3%); myocardial infarction, congestive heart failure,  
607 ischemic retinopathy, Raynaud's phenomenon, hot flashes (<1%).

608 Pulmonary: Pneumonitis, some cases responded to interferon cessation and corticosteroid  
 609 therapy (<5%); chest congestion (<3%); tachypnea (<1%).  
 610 Central Nervous System and Psychiatric: Stroke, coma, encephalopathy, transient ischemic  
 611 attacks, dysphasia, hallucinations, gait disturbance, psychomotor retardation, apathy,  
 612 sedation, irritability, hyperactivity, claustrophobia, loss of libido, ataxia, neuropathy, poor  
 613 coordination, dysarthria, aphasia, aphonia, amnesia (<1%).  
 614 Autoimmune Disease: Vasculitis, arthritis, hemolytic anemia and lupus erythematosus  
 615 syndrome (<3%).  
 616 Other: Thyroid dysfunction including hypothyroidism and hyperthyroidism, diabetes  
 617 requiring insulin therapy in some patients (<5%); anaphylactic reactions, eye irritation,  
 618 earache, cyanosis, flushing of skin (<1%).

### **619 Abnormal Laboratory Test Values**

620 The percentage of patients with chronic hepatitis C, hairy cell leukemia, and with chronic  
 621 myelogenous leukemia who experienced a significant abnormal laboratory test value (*NCI*  
 622 or *WHO* grades III or IV) at least once during their treatment with Roferon-A is shown in  
 623 Table 2:

**624 Table 2 Significant Abnormal Laboratory Test Values**

	<b>Chronic Hepatitis C (n=203) 3 MIU tiw</b>	<b>Chronic Myelogenous Leukemia‡</b>		<b>Hairy Cell Leukemia (n=218)</b>
		<b>US Study (n=91)</b>	<b>Non-US Study (n=219)</b>	
Leukopenia	1.5%	20%	3%	45%*
Neutropenia	10%	22%	0%	68%*
Thrombocytopenia	4.5%	27%	5%	62%*
Anemia (Hb)	0%	15%	4%	31%*
SGOT	NAP	5%	1%	9%
Alk. Phosphatase	0%	3%	1%	3%
LDH	NAP	NA	NA	<1%
Proteinuria	0%	NA	NA	10%†

625 \* In the majority of patients, initial hematologic laboratory test values were abnormal due  
 626 to their underlying disease.  
 627 † Ten percent of the patients experienced a proteinuria >1+ at least once.  
 628 ‡ Patients enrolled in the two clinical studies receiving at least one dose of Roferon-A.  
 629 NAP = Not applicable.  
 630 NA = Not assessed.

631 Elevated triglyceride levels have been observed in patients receiving interferon therapy,  
632 including Roferon-A.

### 633 **Chronic Hepatitis C**

634 The incidence of neutropenia (*WHO grades III or IV*) was over twice as high in those  
635 treated with 6 MIU tiw (21%) as those treated with 3 MIU tiw (10%).

### 636 **Chronic Myelogenous Leukemia**

637 In the two clinical studies, a severe or life-threatening anemia was seen in up to 15% of  
638 patients. A severe or life-threatening leukopenia and thrombocytopenia were observed in  
639 up to 20% and 27% of patients, respectively. Changes were usually reversible when  
640 therapy was discontinued. One case of aplastic anemia and one case of Coombs' positive  
641 hemolytic anemia were seen in 310 patients treated with rIFN $\alpha$ -2a in clinical studies.  
642 Severe cytopenias led to discontinuation of therapy in 4% of all Roferon-A treated patients.

643 Transient increases in liver transaminases or alkaline phosphatase of any intensity were  
644 seen in up to 50% of patients during treatment with Roferon-A. Only 5% of patients had a  
645 severe or life-threatening increase in SGOT. In the clinical studies, such abnormalities  
646 required termination of therapy in less than 1% of patients.

### 647 **Hairy Cell Leukemia**

648 Increases in serum phosphorus ( $\geq 1.6$  mmol/L) and serum uric acid ( $\geq 9.1$  mg/dL) were  
649 observed in 9% and 10% of patients, respectively. The increase in serum uric acid is likely  
650 to be related to the underlying disease. Decreases in serum calcium ( $\leq 1.9$  mmol/L) and  
651 serum phosphorus ( $\leq 0.9$  mmol/L) were seen in 28% and 22% of patients, respectively.

### 652 **Postmarketing**

653 Central and Peripheral Nervous System: Somnolence, hearing impairment, hearing loss.

654 Vision: Retinopathy including retinal hemorrhages and cotton-wool spots, papilledema,  
655 retinal artery and vein thrombosis and optic neuropathy.

656 Skin: Injection site necrosis.

657 Blood: Idiopathic thrombocytopenic purpura, cyanosis.

658 Renal and Urinary System: Increased blood urea and serum creatinine, decreased renal  
659 function and acute renal failure.

660 Endocrine: Hyperglycemia.

661 Immune System Disorder: Sarcoidosis.

662 Respiratory: Pulmonary edema.

663 Metabolic and Nutritional: Cases of hypertriglyceridemia/hyperlipidemia have been  
664 reported including some occurring in association with pancreatitis.

665 **OVERDOSAGE**

666 There are no reports of overdosage, but repeated large doses of interferon can be associated  
667 with profound lethargy, fatigue, prostration, and coma. Such patients should be hospitalized  
668 for observation and appropriate supportive treatment given.

669 **DOSAGE AND ADMINISTRATION**

670 Roferon-A recommended dosing regimens are different for each of the following  
671 indications as described below.

672 *Note:* Parenteral drug products should be inspected visually for particulate matter and  
673 discoloration before administration, whenever solution and container permit.

674 Roferon-A is administered subcutaneously.

675 **Chronic Hepatitis C**

676 The recommended dosage of Roferon-A for the treatment of chronic hepatitis C is 3 MIU  
677 three times a week (tiw) administered subcutaneously for 12 months (48 to 52 weeks). As  
678 an alternative, patients may be treated with an induction dose of 6 MIU tiw for the first 3  
679 months (12 weeks) followed by 3 MIU tiw for 9 months (36 weeks). Normalization of  
680 serum ALT generally occurs within a few weeks after initiation of treatment in responders.  
681 Approximately 90% of patients who respond to Roferon-A do so within the first 3 months  
682 of treatment; however, patients responding to Roferon-A with a reduction in ALT should  
683 complete 12 months of treatment. Patients who have no response to Roferon-A within the  
684 first 3 months of therapy are not likely to respond with continued treatment; treatment  
685 discontinuation should be considered in these patients.

686 Patients who tolerate and partially or completely respond to therapy with Roferon-A but  
687 relapse following its discontinuation may be re-treated. Re-treatment with either 3 MIU tiw  
688 or with 6 MIU tiw for 6 to 12 months may be considered. Please see ADVERSE  
689 REACTIONS regarding the increased frequency of adverse reactions associated with  
690 treatment with higher doses.

691 Temporary dose reduction by 50% is recommended in patients who do not tolerate the  
692 prescribed dose. If adverse events resolve, treatment with the original prescribed dose can  
693 be re-initiated. In patients who cannot tolerate the reduced dose, cessation of therapy, at  
694 least temporarily, is recommended.

695 **Chronic Myelogenous Leukemia**

696 For patients with Ph-positive CML in chronic phase: Prior to initiation of therapy, a  
697 diagnosis of Philadelphia chromosome positive CML in chronic phase by the appropriate  
698 peripheral blood, bone marrow and other diagnostic testing should be made. Monitoring of  
699 hematologic parameters should be done regularly (e.g., monthly). Since significant  
700 cytogenetic changes are not readily apparent until after hematologic response has occurred,  
701 and usually not until several months of therapy have elapsed, cytogenetic monitoring may  
702 be performed at less frequent intervals. Achievement of complete cytogenetic response has  
703 been observed up to 2 years following the start of Roferon-A treatment.

704 The recommended initial dose of Roferon-A is 9 MIU daily administered as a  
705 subcutaneous injection. Based on clinical experience,<sup>3</sup> short-term tolerance may be  
706 improved by gradually increasing the dose of Roferon-A over the first week of  
707 administration from 3 MIU daily for 3 days to 6 MIU daily for 3 days to the target dose of  
708 9 MIU daily for the duration of the treatment period.

709 The optimal dose and duration of therapy have not yet been determined. Even though the  
710 median time to achieve a complete hematologic response was 5 months in study MI400,  
711 hematologic responses have been observed up to 18 months after treatment start. Treatment  
712 should be continued until disease progression. If severe side effects occur, a treatment  
713 interruption or a reduction in either the dose or the frequency of injections may be  
714 necessary to achieve the individual maximally tolerated dose (see **PRECAUTIONS**).

715 Limited data are available on the use of Roferon-A in children with CML. In one report of  
716 15 children with Ph-positive, adult-type CML doses between 2.5 to 5 MIU/m<sup>2</sup>/day given  
717 intramuscularly were tolerated.<sup>8</sup> In another study, severe adverse effects including deaths  
718 were noted in children with previously untreated, Ph-negative, juvenile CML, who received  
719 interferon doses of 30 MIU/m<sup>2</sup>/day.<sup>12</sup>

## 720 **Hairy Cell Leukemia**

721 Prior to initiation of therapy, tests should be performed to quantitate peripheral blood  
722 hemoglobin, platelets, granulocytes and hairy cells and bone marrow hairy cells. These  
723 parameters should be monitored periodically (e.g., monthly) during treatment to determine  
724 whether response to treatment has occurred. If a patient does not respond within 6 months,  
725 treatment should be discontinued. If a response to treatment does occur, treatment should  
726 be continued until no further improvement is observed and these laboratory parameters  
727 have been stable for about 3 months. Patients with hairy cell leukemia have been treated for  
728 up to 24 consecutive months. The optimal duration of treatment for this disease has not  
729 been determined.

730 The induction dose of Roferon-A is 3 MIU daily for 16 to 24 weeks, administered as a  
731 subcutaneous injection. The recommended maintenance dose is 3 MIU, tiw. Dose reduction  
732 by one-half or withholding of individual doses may be needed when severe adverse  
733 reactions occur. The use of doses higher than 3 MIU is not recommended in hairy cell  
734 leukemia.

## 735 **HOW SUPPLIED**

### 736 **Single Use Prefilled Syringes**

737 (for subcutaneous administration)

738     *3 million IU Roferon-A per syringe* — Each 0.5 mL contains 3 MIU of Interferon  
739        alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg  
740        benzyl alcohol as a preservative and 0.385 mg ammonium acetate. Boxes of 1  
741        (NDC 0004-2015-09); Boxes of 6 (NDC 0004-2015-07).

742     *6 million IU Roferon-A per syringe* — Each 0.5 mL contains 6 MIU of Interferon  
743        alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg

744       benzyl alcohol as a preservative and 0.385 mg ammonium acetate. Boxes of 1  
745       (NDC 0004-2016-09); Boxes of 6 (NDC 0004-2016-07).

746       *9 million IU Roferon-A per syringe* — Each 0.5 mL contains 9 MIU of Interferon  
747       alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg  
748       benzyl alcohol as a preservative and 0.385 mg ammonium acetate. Boxes of 1  
749       (NDC 0004-2017-09); Boxes of 6 (NDC 0004-2017-07).

750       **Storage**

751       The prefilled syringe should be stored in the refrigerator at 36° to 46°F (2° to 8°C). Do *not*  
752       freeze or shake. Protect Roferon-A from light during storage.

753       **REFERENCES**

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766       Revised: January 2008

767

## MEDICATION GUIDE

769

### Roferon -A

770

(Interferon alfa-2a, recombinant)

771

### Solution for Injection – Prefilled Syringes

772

773 Before you start taking Roferon-A (ro-FER-on), please read this Medication Guide  
774 carefully. Read this Medication Guide each time you refill your prescription in case new  
775 information has been added. This information does not take the place of talking with your  
776 healthcare provider.

#### **What is the most important information I should know about Roferon-A?**

779 Roferon-A is used to treat people with hepatitis C, hairy cell leukemia and Philadelphia  
780 chromosome positive chronic myelogenous leukemia (CML). However, Roferon-A can  
781 cause some serious side effects that may cause death in rare cases. Before starting  
782 Roferon-A, you should talk with your healthcare provider about the possible benefits and  
783 the possible side effects of treatment, to decide if Roferon-A is right for you. While  
784 taking Roferon-A, you will need to see your healthcare provider regularly for medical  
785 examinations and blood tests to make sure your treatment is working and to check for  
786 side effects.

787 The most serious possible side effects of Roferon-A treatment include:

- 788 1. **Mental health problems:** Roferon-A may cause some patients to develop mood or  
789 behavioral problems. Signs of these problems include irritability (getting easily upset),  
790 depression (feeling low, feeling bad about yourself or feeling hopeless), and anxiety.  
791 Some patients may have aggressive behavior and think about hurting others. Some  
792 patients may develop thoughts about ending their lives (suicidal thoughts) and may  
793 attempt to do so. A few patients have even ended their lives. Former drug addicts may  
794 fall back into drug addiction or overdose. You must tell your healthcare provider if  
795 you are being treated for a mental illness or have a history of mental illness or if you  
796 are or have ever been addicted to drugs or alcohol. Call your healthcare provider  
797 immediately if you develop any of these problems while on Roferon-A treatment.
- 798 2. **Heart problems:** Roferon-A may cause some patients to experience high blood  
799 pressure, a fast heartbeat, chest pain, and very rarely a heart attack. Tell your  
800 healthcare provider if you have or have had any heart problems in the past.
- 801 3. **Blood problems:** Many patients taking Roferon-A have had a drop in the number of  
802 their white blood cells and their platelets. If the numbers of these blood cells are too  
803 low, you could be at risk for infections or bleeding.

804 **Stop taking Roferon-A and call your healthcare provider immediately if you  
805 develop any of these symptoms:**

- 806 • You become very depressed or think about suicide
- 807 • You have severe chest pain
- 808 • You have trouble breathing
- 809 • You have a change in your vision
- 810 • You notice unusual bleeding or bruising
- 811 • High fever
- 812 • Severe stomach pain. If the pain is in the lower part of your stomach area it  
813 could mean that your bowels are inflamed (colitis)

814 *For more information on possible side effects with Roferon-A therapy, please read the  
815 section on "What are the possible side effects of Roferon-A?" in this Medication Guide.*

816 **What is Roferon-A?**

817 Roferon-A is a treatment that is used for some people who are infected with the hepatitis  
818 C virus, hairy cell leukemia, and Philadelphia chromosome positive chronic myelogenous  
819 leukemia (CML). Patients with hepatitis C have the virus that causes hepatitis in their  
820 blood and liver. Patients with hairy cell leukemia produce abnormal white blood cells that  
821 travel to the spleen where they trap and destroy normal blood cells. In CML, your body  
822 produces too many of certain blood cells. Roferon-A works in these conditions by  
823 reducing the amount of virus in the body, destroying cells that may be harmful to your  
824 body and keeping the body from producing too many cells.

825 **Who should not take Roferon-A?**

826 Do not use Roferon-A if:

- 827 • You are pregnant or breast-feeding or are planning to become pregnant.
- 828 • You are allergic to alpha interferons, *Escherichia coli*-derived products or any  
829 component of Roferon-A.
- 830 • You have autoimmune hepatitis (hepatitis caused by your immune system attacking  
831 your liver).

832 Roferon-A should not be given to newborn or premature infants.

833 **If you have or have had any of the following conditions or serious medical problems,  
834 discuss them with your doctor before taking Roferon-A:**

- 835 • History of or current severe mental illness (such as depression or anxiety)
- 836 • Previous heart attack or heart problems
- 837 • Sleep problems
- 838 • High blood pressure
- 839 • Autoimmune disease (where the body's immune system attacks the body's own  
840 cells), such as vasculitis, psoriasis, systemic lupus erythematosus, rheumatoid arthritis
- 841 • Kidney problems

- Blood disorders-Low blood counts or bleeding problems
- You take a medicine called theophylline
- Diabetes (high blood sugar)
- Thyroid problems
- Liver problems, other than hepatitis C
- Hepatitis B infection
- HIV infection (the virus that causes AIDS)
- Problems with your vision
- Colitis
- Body organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)
- Alcoholism
- Drug abuse or addiction

If you have any doubts about your health condition or about taking Roferon-A, talk to your healthcare provider.

### **What should I avoid while taking Roferon-A?**

- Female patients as well as female partners of male patients must avoid becoming pregnant while taking Roferon-A. Roferon-A may harm your unborn child or cause you to lose your baby (miscarry).
- You should not breast-feed your baby while taking Roferon-A.

### **How should I take Roferon-A?**

To get the most benefit from this medicine, it is important to take Roferon-A exactly as your healthcare provider tells you.

Your healthcare provider will tell you how much medicine to take and how often to take it. Once you start treatment with Roferon-A, do not switch to another brand of interferon without talking to your doctor. Other interferons may not have the same effect on the treatment of your disease. Switching brands will also require a change in your dose. Your healthcare provider will tell you how long you need to use Roferon-A.

Over time, your healthcare provider may change your dose of Roferon-A. Do not change your dose unless your doctor tells you to change it.

Roferon-A is supplied in prefilled syringes. Whether you give yourself the injection or another person gives the injection to you, it is important to follow the instructions in this Medication Guide (see the appendix "Instructions for Preparing and Giving a Dose with a Roferon-A Prefilled Syringe").

If you miss a dose of Roferon-A, take the missed dose as soon as possible during the same day or the next day, then continue on your regular dosing schedule. If several days go by after you miss a dose, check with your doctor about what to do. Do not double the next dose or take more than one dose a day unless your doctor tells you to. Call your

881 doctor right away if you take more than your prescribed Roferon-A dose. Your doctor  
882 may wish to examine you more closely and take blood for testing.

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

885 Tell your doctor if you are taking or planning to take other prescription or non-  
886 prescription medicines, including vitamins and mineral supplements and herbal  
887 medicines.

888 **What are the possible side effects of Roferon-A?**

889 Possible, serious side effects include:

- 890 • **Mental health problems including suicide, suicidal thoughts, heart problems, and blood problems:** See the section "What is the most important information I  
891 should know about Roferon-A?".
- 893 • **Other body organ problems:** Some patients may experience lung problems (such as  
894 difficulty breathing or pneumonia) and vision problems.
- 895 • **New or worsening autoimmune disease:** Some patients may develop an  
896 autoimmune disease (a disease where the body's own immune system begins to attack  
897 itself) while on Roferon-A therapy. These diseases can include vasculitis (an  
898 inflammation of your blood vessels), rheumatoid arthritis or lupus erythematosus,  
899 psoriasis or thyroid problems. In some patients who already have an autoimmune  
900 disease, the disease may worsen while on Roferon-A therapy.

901

902 Common, but less serious, side effects include:

- 903 • **Flu-like symptoms:** Most patients who take Roferon-A have flu-like symptoms that  
904 usually lessen after the first few weeks of treatment. Flu-like symptoms may include  
905 unusual tiredness, fever, chills, muscle aches, and joint pain. Taking acetaminophen  
906 or ibuprofen before you take Roferon-A can help with these symptoms. You can also  
907 try taking Roferon-A at night. You may be able to sleep through the symptoms.
- 908 • **Extreme fatigue (tiredness):** Many patients may become extremely tired while on  
909 Roferon-A therapy.
- 910 • **Upset stomach:** Nausea, taste changes, diarrhea, and loss of appetite occur  
911 commonly.
- 912 • **Blood sugar problems:** Some patients may develop a problem with the way their  
913 body controls their blood sugar and may develop diabetes.
- 914 • **Thyroid problems:** Some patients may develop changes in their thyroid function.  
915 Symptoms of these changes may include feeling hot or cold all the time, trouble  
916 concentrating, changes in your skin (your skin may become very dry), and changes in  
917 your weight.
- 918 • **Skin reactions:** Some patients may develop a rash, dry or itchy skin, and redness and  
919 swelling at the site of injection.
- 920 • **Sleep disturbances and headache:** Trouble sleeping and headaches may also occur  
921 during Roferon-A therapy.

- 922     • **Hair thinning:** Hair loss is not uncommon while using Roferon-A. This hair loss is  
923       temporary and hair growth should return after you stop taking Roferon-A.  
924
- 925       These are not all of the side effects of Roferon-A. Your doctor or pharmacist can give  
926       you a more complete list.
- 927       Talk to your healthcare provider if you are worried about side effects or find them very  
928       bothersome.
- 929       **General advice about prescription medicines**
- 930       Medicines are sometimes prescribed for purposes other than those listed in a Medication  
931       Guide. If you have any concerns or questions about Roferon-A, contact your healthcare  
932       provider. Do not use Roferon-A for a condition or person other than that for which it is  
933       prescribed. If you want to know more about Roferon-A, your healthcare provider or  
934       pharmacist will be able to provide you with detailed information that is written for  
935       healthcare providers.
- 936       This Medication Guide has been approved by the U.S. Food and Drug Administration.
- 937       Keep this and all other medications out of the reach of children.
- 938       Revised: October 2004

939  
940     **Medication Guide Appendix: Instructions for Preparing and Giving a Dose**  
941                 **with a Roferon-A Prefilled Syringe**

942     **How should I store Roferon-A?**

943     Roferon-A must be stored in the refrigerator at a temperature of 36°F to 46°F (2°C to  
944     8°C). Do not leave Roferon-A outside of the refrigerator for more than 24 hours. Do not  
945     freeze Roferon-A. Keeping Roferon-A at temperatures outside the recommended range  
946     can destroy the medicine. Do not shake Roferon-A. Shaking can destroy Roferon-A so  
947     that it will not work. Protect Roferon-A from light during storage.

948     **How do I inject Roferon-A?**

949     The instructions that follow will help you learn how to use Roferon-A prefilled syringes.  
950     Please read all of these directions before trying to take your medicine. It is important to  
951     follow these directions carefully. Talk to your healthcare provider if you have any  
952     concerns about how to use Roferon-A. Whether you are giving yourself an injection or if  
953     you are giving this injection to someone else, a healthcare provider must teach you how  
954     to inject.

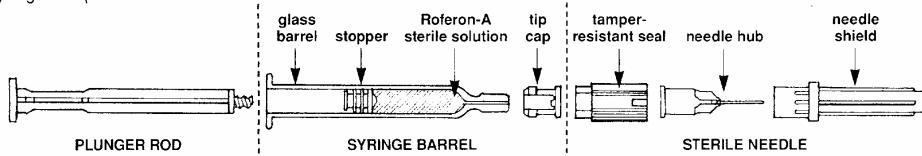
955     **The prefilled syringes are used for injecting Roferon-A under the surface of the skin  
956     (subcutaneous).**

- 957     1. Collect all the materials you will need before you start to give the injection:
  - 958         • one sterile Roferon-A prefilled syringe with needle
  - 959         • alcohol swabs
  - 960         • puncture-resistant disposable container
- 961     2. Check the expiration date on the package to make sure that it has not passed and  
962         check the solution in the syringe. The solution in the syringe should be clear or  
963         colorless to light yellow in color.
  - 964         • Do not use Roferon-A if:
    - 965             – the medicine is cloudy
    - 966             – the medicine has particles floating in it
    - 967             – the medicine is any color besides clear or colorless to light yellow
    - 968             – it has passed the expiration date
- 969     3. Warm the refrigerated medicine by gently rolling the syringe in the palms of your  
970         hands for about one minute.
- 971     4. Wash your hands with soap and warm water. This step is very important to help  
972         prevent infection.
- 973     5. Roferon-A prefilled syringe:

---

**ASSEMBLY INSTRUCTIONS FOR ROFERON-A PREFILLED SYRINGE**

Syringe components:

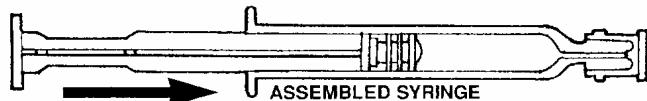


974

975 6. Assemble syringe:

- 976     • Place the plunger rod into the open end of the syringe barrel.
- 977     • Gently screw the rod into the plunger stopper until snug.  
978       DO NOT USE FORCE.

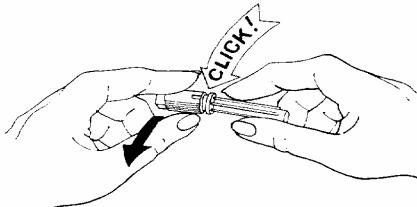
979



980 7. Prepare the needle:

- 981     • Turn and pull off the bright yellow tamper-resistant seal from needle. A  
982       “click” sound means that the needle is OK to use.

983



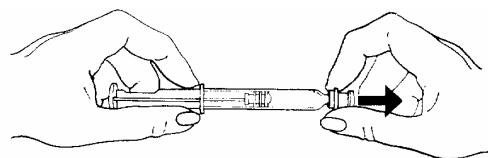
984

985       IF YOU DO NOT HEAR A “CLICK”, DO NOT USE THE NEEDLE AND DO  
986       NOT REMOVE THE CLEAR NEEDLE SHIELD. DISCARD THE NEEDLE IN  
THE PUNCTURE-PROOF CONTAINER.

987

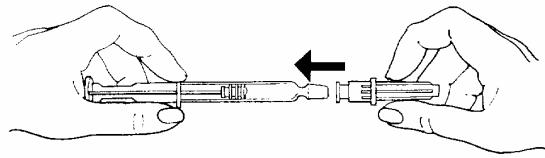
988       If you have another needle, proceed again with Step 7. If no alternate needle is  
989       available, contact your healthcare provider to make arrangements for a replacement  
needle.

990 8. To attach the needle to the prefilled syringe:



991

992 • Remove the grey tip cap from syringe barrel.



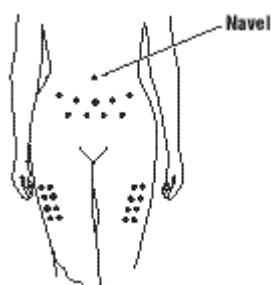
993

994 • Place the needle onto the end of the syringe barrel so it fits snugly. Do not  
995 remove the clear needle shield.

996 9. Choose an injection site:

997 • You should choose a different spot each time you give or receive an injection.  
998 The common sites to use are:

- 999 • abdomen, avoiding the navel and waistline area  
1000 • thigh



1001

1002 • If someone else is giving you the injection, then the upper, outer arm can be  
1003 used as an injection site.



1004

1005

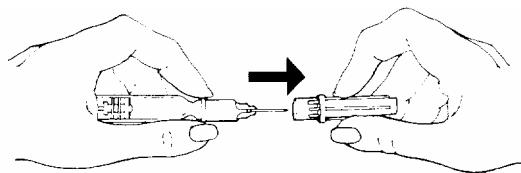
1006

1007 10. Preparing the injection site:

- 1008 • Clean the skin where the injection will be given with an alcohol swab and  
1009 allow the site to dry for 10 seconds.

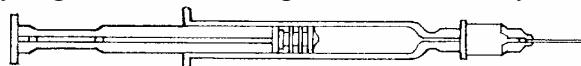
1010 11. Injecting Roferon-A:

- 1011 • Hold the pale yellow hub between your thumb and forefinger and carefully (to  
1012 avoid a needle-stick) remove the clear needle shield with your other hand. The  
1013 syringe is ready for injection.



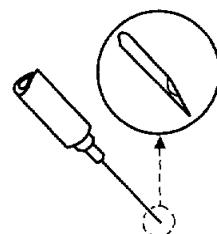
1014

- 1015 • Keep the syringe in a horizontal position until ready for use.



1016

- 1017 • Holding the syringe with the needle facing up, tap the syringe barrel to bring  
1018 air bubbles to the top.  
1019 • Press the plunger slightly to push the air bubbles out through the needle.  
1020 • Hold the syringe horizontally, and position the bevel of the needle so the point  
1021 of the needle is facing up.



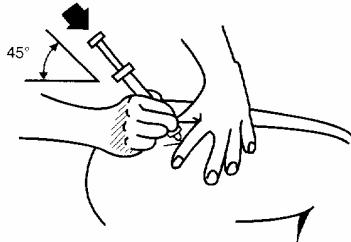
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- 1023 • Pinch an area of skin firmly between your thumb and forefinger.



1024

- 1025           • Hold the needle like a pencil at a 45° to 90° angle to skin and using a quick  
1026            dart-like motion, insert the needle as far as it will go.

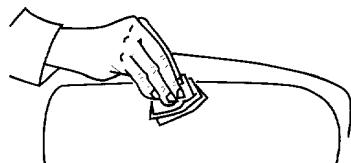


1027

- 1028           • Once inserted, draw back slowly on the syringe. If blood appears in the  
1029            syringe, the needle has entered a blood vessel.

1030   **Do not inject Roferon-A at that site and discard the syringe. Use a new syringe for**  
1031   **the injection and use at a different injection site.**

- 1032           • If blood does not appear in the syringe then slowly push the plunger all the  
1033            way down so that you get all of your medicine.
- 1034           • Withdraw the needle at same angle it was inserted. See instructions for  
1035            disposal of the needle and syringe in the section "How should I dispose of  
1036            materials used to inject Roferon-A?".
- 1037           • When you are finished, place an alcohol swab over the injection site and press  
1038            slightly.



1039

- 1040           • Do not reuse syringes and needles. Use a new prefilled syringe and needle for  
1041            each injection.

**1042   How should I dispose of materials used to inject Roferon-A?**

- 1043           • Do not recap the needle.
- 1044           • Place the entire syringe and needle in a puncture-resistant container. A home "Sharps  
1045            Container" may be purchased at your pharmacy or you can use a hard plastic  
1046            container with a screw top or a coffee can with a plastic lid. You should talk to your  
1047            healthcare provider about how to properly dispose of a full container of used syringes.  
1048            There may be special state or local laws about disposing used syringes and needles,  
1049            so please check with your physician, nurse or pharmacist for instructions. DO NOT  
1050            throw the filled container in the household trash and DO NOT recycle.

- 1051 • The needle cover and alcohol swabs can be thrown in the regular trash. You should  
1052 always keep your syringes and disposal container out of the reach of children.

1053 Appendix revision date: September 2003

1054



**Pharmaceuticals**

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