

1 **10-27-04-Final Draft PI**

2 F-XXXXXXXXXX

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4 **PRODUCT
INFORMATION**5 **INTRON® A**
6 **Interferon alfa-2b,**
7 **recombinant**
8 **For Injection**
910 **WARNING**11 Alpha interferons, including INTRON® A, cause or aggravate fatal or life-threatening
12 neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should
13 be monitored closely with periodic clinical and laboratory evaluations. Patients with
14 persistently severe or worsening signs or symptoms of these conditions should be
15 withdrawn from therapy. In many but not all cases these disorders resolve after
16 stopping INTRON A therapy. See **WARNINGS** and **ADVERSE REACTIONS**17
18 **DESCRIPTION**19 INTRON A for intramuscular, subcutaneous, intralesional, or intravenous Injection is
20 a purified sterile recombinant interferon product.21 Interferon alfa-2b, recombinant for Injection has been classified as an alfa
22 interferon and is a water-soluble protein with a molecular weight of 19,271 daltons
23 produced by recombinant DNA techniques. It is obtained from the bacterial
24 fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid
25 containing an interferon alfa-2b gene from human leukocytes. The fermentation is
26 carried out in a defined nutrient medium containing the antibiotic tetracycline
27 hydrochloride at a concentration of 5 to 10 mg/L; the presence of this antibiotic is not
28 detectable in the final product. The specific activity of Interferon alfa-2b,
29 recombinant is approximately 2.6×10^8 IU/mg protein as measured by the HPLC
30 assay.**Powder for Injection**

Vial Strength Million IU	mL Diluent	Final Concentration after Reconstitution million IU/mL	mg INTRON A [†] Interferon alfa-2b, recombinant per vial	Route of Administration
10	1	10	0.038	IM, SC, IV, IL
18	1	18	0.069	IM, SC, IV
50	1	50	0.192	IM, SC, IV

* Each mL also contains 20 mg glycine, 2.3 mg sodium phosphate dibasic, 0.55 mg sodium phosphate monobasic, and 1.0 mg human albumin.

† Based on the specific activity of approximately 2.6×10^8 IU/mg protein, as measured by HPLC assay.31 Prior to administration, the INTRON A Powder for Injection is to be reconstituted with
32 the provided Diluent for INTRON A (Sterile Water for Injection, USP) (see **DOSAGE**

33 **AND ADMINISTRATION).** INTRON A Powder for Injection is a white to cream-
34 colored powder.

Solution Vials for Injection

Vial Strength	Concentration*	mg INTRON A [†] per vial	Route of Administration
10 MIU single dose	10 million IU/1.0 mL	0.038	SC, IL
18 [‡] MIU multidose	3 million IU/0.5 mL	0.088	IM, SC
25 [¶] MIU multidose	5 million IU/0.5 mL	0.123	IM, SC, IL

* Each mL contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.

[†] Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay.

[‡] This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b, recombinant per 3.8 mL in order to provide the delivery of six 0.5-mL doses, each containing 3 million IU of INTRON A Interferon alfa-2b, recombinant for Injection (for a label strength of 18 million IU).

[¶] This is a multidose vial which contains a total of 32.0 million IU of interferon alfa-2b, recombinant per 3.2 mL in order to provide the delivery of five 0.5-mL doses, each containing 5 million IU of INTRON A Interferon alfa-2b, recombinant for Injection (for a label strength of 25 million IU).

35

Solution in Multidose Pens for Injection

Pen Strength	Concentration*	INTRON A Dose Delivered (6 doses, 0.2 mL each)	mg INTRON A [†] Interferon alfa- 2b, recombinant per 1.5ml	Route of Administration
3MIU	22.5	3 MIU/0.2ml	0.087	SC
5 MIU	37.5	5 MIU/0.2ml	0.144	SC
10 MIU	75	10 MIU/0.2ml	0.288	SC

* Each mL also contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.

[†] Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay.

36

37 These packages do not require reconstitution prior to administration (see **DOSAGE**
38 **AND ADMINISTRATION)** INTRON A Solution for Injection is a clear, colorless
39 solution.

40

41 **CLINICAL PHARMACOLOGY**

42 **General** The interferons are a family of naturally occurring small proteins and
43 glycoproteins with molecular weights of approximately 15,000 to 27,600 daltons
44 produced and secreted by cells in response to viral infections and to synthetic or
45 biological inducers.

46

47 Preclinical Pharmacology Interferons exert their cellular activities by binding
to specific membrane receptors on the cell surface. Once bound to the cell



48 membrane, interferons initiate a complex sequence of intracellular events. *In vitro*
49 studies demonstrated that these include the induction of certain enzymes,
50 suppression of cell proliferation, immunomodulating activities such as enhancement
51 of the phagocytic activity of macrophages and augmentation of the specific
52 cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-
53 infected cells.

54 In a study using human hepatoblastoma cell line, HB 611, the *in vitro* antiviral
55 activity of alfa interferon was demonstrated by its inhibition of hepatitis B virus (HBV)
56 replication.

57 The correlation between these *in vitro* data and the clinical results is
58 unknown. Any of these activities might contribute to interferon's therapeutic effects.

59 Pharmacokinetics The pharmacokinetics of INTRON A were studied in 12
60 healthy male volunteers following single doses of 5 million IU/m² administered
61 intramuscularly, subcutaneously, and as a 30-minute intravenous infusion in a
62 crossover design.

63 The mean serum INTRON A concentrations following intramuscular and
64 subcutaneous injections were comparable. The maximum serum concentrations
65 obtained via these routes were approximately 18 to 116 IU/mL and occurred 3 to
66 12 hours after administration. The elimination half-life of INTRON A following both
67 intramuscular and subcutaneous injections was approximately 2 to 3 hours. Serum
68 concentrations were undetected by 16 hours after the injections.

69 After intravenous administration, serum INTRON A concentrations peaked
70 (135 to 273 IU/mL) by the end of the 30-minute infusion, then declined at a slightly
71 more rapid rate than after intramuscular or subcutaneous drug administration,
72 becoming undetectable 4 hours after the infusion. The elimination half-life was
73 approximately 2 hours.

74 Urine INTRON A concentrations following a single dose (5 million IU/m²) were
75 not detectable after any of the parenteral routes of administration. This result was
76 expected since preliminary studies with isolated and perfused rabbit kidneys have
77 shown that the kidney may be the main site of interferon catabolism.

78 There are no pharmacokinetic data available for the intralesional route of
79 administration.

80 Serum Neutralizing Antibodies In INTRON A treated patients tested for
81 antibody activity in clinical trials, serum anti-interferon neutralizing antibodies were
82 detected in 0% (0/90) of patients with hairy cell leukemia, 0.8% (2/260) of patients
83 treated intralesionally for condylomata acuminata, and 4% (1/24) of patients with
84 AIDS-Related Kaposi's Sarcoma. Serum neutralizing antibodies have been detected
85 in <3% of patients treated with higher INTRON A doses in malignancies other than
86 hairy cell leukemia or AIDS-Related Kaposi's Sarcoma. The clinical significance of
87 the appearance of serum anti-interferon neutralizing activity in these indications is
88 not known.

89 Serum anti-interferon neutralizing antibodies were detected in 7% (12/168) of
90 patients either during treatment or after completing 12 to 48 weeks of treatment with
91 3 million IU TIW of INTRON A therapy for chronic hepatitis C and in 13% (6/48) of
92 patients who received INTRON A therapy for chronic hepatitis B at 5 million IU QD
93 for 4 months, and in 3% (1/33) of patients treated at 10 million IU TIW. Serum anti-



94 interferon neutralizing antibodies were detected in 9% (5/53) of pediatric patients
95 who received INTRON A therapy for chronic hepatitis B at 6 million IU/m² TIW.
96 Among all chronic hepatitis B or C patients, pediatric and adults with detectable
97 serum neutralizing antibodies, the titers detected were low (22/24 with titers \leq 1:40
98 and 2/24 with titers \leq 1:160). The appearance of serum anti-interferon neutralizing
99 activity did not appear to affect safety or efficacy.

100
101 **Hairy Cell Leukemia** In clinical trials in patients with hairy cell leukemia, there was
102 depression of hematopoiesis during the first 1 to 2 months of INTRON A treatment,
103 resulting in reduced numbers of circulating red and white blood cells, and platelets.
104 Subsequently, both splenectomized and nonsplenectomized patients achieved
105 substantial and sustained improvements in granulocytes, platelets, and hemoglobin
106 levels in 75% of treated patients and at least some improvement (minor responses)
107 occurred in 90%. INTRON A treatment resulted in a decrease in bone marrow
108 hypercellularity and hairy cell infiltrates. The hairy cell index (HCI), which represents
109 the percent of bone marrow cellularity times the percent of hairy cell infiltrate, was
110 \geq 50% at the beginning of the study in 87% of patients. The percentage of patients
111 with such an HCI decreased to 25% after 6 months and to 14% after 1 year. These
112 results indicate that even though hematologic improvement had occurred earlier,
113 prolonged INTRON A treatment may be required to obtain maximal reduction in
114 tumor cell infiltrates in the bone marrow.

115 The percentage of patients with hairy cell leukemia who required red blood
116 cell or platelet transfusions decreased significantly during treatment and the
117 percentage of patients with confirmed and serious infections declined as granulocyte
118 counts improved. Reversal of splenomegaly and of clinically significant
119 hypersplenism was demonstrated in some patients.

120 A study was conducted to assess the effects of extended INTRON A
121 treatment on duration of response for patients who responded to initial therapy. In
122 this study, 126 responding patients were randomized to receive additional
123 INTRON A treatment for 6 months or observation for a comparable period, after
124 12 months of initial INTRON A therapy. During this 6-month period, 3% (2/66) of
125 INTRON A treated patients relapsed compared with 18% (11/60) who were not
126 treated. This represents a significant difference in time to relapse in favor of
127 continued INTRON A treatment ($p=0.006/0.01$, Log Rank/Wilcoxon). Since a small
128 proportion of the total population had relapsed, median time to relapse could not be
129 estimated in either group. A similar pattern in relapses was seen when all
130 randomized treatment, including that beyond 6 months, and available follow-up data
131 were assessed. The 15% (10/66) relapses among INTRON A patients occurred
132 over a significantly longer period of time than the 40% (24/60) with observation
133 ($p=0.0002/0.0001$, Log Rank/Wilcoxon). Median time to relapse was estimated,
134 using the Kaplan-Meier method, to be 6.8 months in the observation group but could
135 not be estimated in the INTRON A group.

136 Subsequent follow-up with a median time of approximately 40 months
137 demonstrated an overall survival of 87.8%. In a comparable historical control group
138 followed for 24 months, overall median survival was approximately 40%.

139



140 **Malignant Melanoma** The safety and efficacy of INTRON A was evaluated as
141 adjuvant to surgical treatment in patients with melanoma who were free of disease
142 (post surgery) but at high risk for systemic recurrence. These included patients with
143 lesions of Breslow thickness >4 mm, or patients with lesions of any Breslow
144 thickness with primary or recurrent nodal involvement. In a randomized controlled
145 trial in 280 patients, 143 patients received INTRON A therapy at 20 million IU/m²
146 intravenously five times per week for 4 weeks (induction phase) followed by 10
147 million IU/m² subcutaneously three times per week for 48 weeks (maintenance
148 phase). In the clinical trial, the median daily INTRON A dose administered to
149 patients was 19.1 million IU/m² during the induction phase and 9.1 million IU/m²
150 during the maintenance phase. INTRON A therapy was begun ≤56 days after
151 surgical resection. The remaining 137 patients were observed.

152 INTRON A therapy produced a significant increase in relapse-free and overall
153 survival. Median time to relapse for the INTRON A treated patients vs. observation
154 patients were 1.72 years vs 0.98 years (p<0.01, stratified Log Rank). The estimated
155 5-year relapse-free survival rate was 37% for INTRON A treated patients vs 26% for
156 observation patients. Median overall survival time for INTRON A treated patients vs
157 observation patients was 3.82 years vs 2.78 years (p=0.047, stratified Log Rank).
158 The estimated 5-year overall survival rate, using the Kaplan-Meier method was 46%
159 for INTRON A treated patients vs 37% for observation patients.

160
161 In a second study of 642 resected high-risk melanoma patients, subjects were
162 randomized equally to one of three groups: high-dose INTRON A therapy for 1 year
163 (same schedule as above), low-dose INTRON A therapy for 2 years (3 MU/d TIW
164 SC), and observation. Consistent with the earlier trial, high-dose INTRON A therapy
165 demonstrated an improvement in relapse-free survival (3-year estimated RFS 48%
166 vs 41%; median RFS 2.4 vs 1.6 years, p = not significant). Relapse-free survival in
167 the low-dose INTRON A arm was similar to that seen in the observation arm.
168 Neither high-dose nor low-dose INTRON A therapy showed a benefit in overall
169 survival as compared to observation in this study.

170
171 **Follicular Lymphoma** The safety and efficacy of INTRON A in conjunction with
172 CHVP, a combination chemotherapy regimen, was evaluated as initial treatment in
173 patients with clinically aggressive, large tumor burden, Stage III/IV follicular Non-
174 Hodgkin's Lymphoma. Large tumor burden was defined by the presence of any one
175 of the following: a nodal or extranodal tumor mass with a diameter of >7 cm;
176 involvement of at least three nodal sites (each with a diameter of >3 cm); systemic
177 symptoms; splenomegaly; serous effusion, orbital or epidural involvement; ureteral
178 compression; or leukemia.

179 In a randomized controlled trial 130 patients received CHVP therapy and
180 135 patients received CHVP therapy plus INTRON A therapy at 5 million IU
181 subcutaneously three times weekly for the duration of 18 months. CHVP
182 chemotherapy consisted of cyclophosphamide 600 mg/m², doxorubicin 25 mg/m²,
183 and teniposide (VM-26) 60 mg/m², administered intravenously on Day 1 and
184 prednisone at a daily dose of 40 mg/m² given orally on Days 1 to 5. Treatment
185 consisted of six CHVP cycles administered monthly, followed by an additional



186 6 cycles administered every 2 months for 1 year. Patients in both treatment groups
187 received a total of 12 CHVP cycles over 18 months.

188 The group receiving the combination of INTRON A therapy plus CHVP had a
189 significantly longer progression-free survival (2.9 years vs 1.5 years, $p=0.0001$, Log
190 Rank test). After a median follow-up of 6.1 years, the median survival for patients
191 treated with CHVP alone was 5.5 years while median survival for patients treated
192 with CHVP plus INTRON A therapy had not been reached ($p=0.004$, Log Rank test).
193 In three additional published, randomized, controlled studies of the addition of
194 interferon alfa to anthracycline-containing combination chemotherapy regimens,¹⁻³
195 the addition of interferon alfa was associated with significantly prolonged
196 progression-free survival. Differences in overall survival were not consistently
197 observed.

198
199 **Condylomata Acuminata** Condylomata acuminata (venereal or genital warts) are
200 associated with infections of the human papilloma virus (HPV). The safety and
201 efficacy of INTRON A in the treatment of condylomata acuminata were evaluated in
202 three controlled double-blind clinical trials. In these studies INTRON A doses of 1
203 million IU per lesion were administered intralesionally three times a week (TIW), in
204 ≤ 5 lesions per patient for 3 weeks. The patients were observed for up to 16 weeks
205 after completion of the full treatment course.

206 INTRON A treatment of condylomata was significantly more effective than
207 placebo, as measured by disappearance of lesions, decreases in lesion size, and by
208 an overall change in disease status. Of 192 INTRON A treated patients and
209 206 placebo treated patients who were evaluable for efficacy at the time of best
210 response during the course of the study, 42% of INTRON A patients vs 17% of
211 placebo patients experienced clearing of all treated lesions. Likewise 24% of
212 INTRON A patients vs 8% of placebo patients experienced marked ($\geq 75\%$ to
213 $< 100\%$) reduction in lesion size, 18% vs 9% experienced moderate ($\geq 50\%$ to $\leq 75\%$)
214 reduction in lesion size, 10% vs 42% had a slight ($< 50\%$) reduction in lesion size,
215 5% vs 24% had no change in lesion size, and 0% vs 1% experienced exacerbation
216 ($p < 0.001$).

217 In one of these studies, 43% (54/125) of patients in whom multiple (≤ 3)
218 lesions were treated, experienced complete clearing of all treated lesions during the
219 course of the study. Of these patients, 81% remained cleared 16 weeks after
220 treatment was initiated.

221 Patients who did not achieve total clearing of all their treated lesions had
222 these same lesions treated with a second course of therapy. During this second
223 course of treatment, 38% to 67% of patients had clearing of all treated lesions. The
224 overall percentage of patients who had cleared all their treated lesions after two
225 courses of treatment ranged from 57% to 85%.

226 INTRON A treated lesions showed improvement within 2 to 4 weeks after the
227 start of treatment in the above study; maximal response to INTRON A therapy was
228 noted 4 to 8 weeks after initiation of treatment.

229 The response to INTRON A therapy was better in patients who had
230 condylomata for shorter durations than in patients with lesions for a longer duration.



231 Another study involved 97 patients in whom three lesions were treated with
232 either an intralesional injection of 1.5 million IU of INTRON A per lesion followed by
233 a topical application of 25% podophyllin, or a topical application of 25% podophyllin
234 alone. Treatment was given once a week for 3 weeks. The combined treatment of
235 INTRON A Interferon alfa-2b, recombinant for Injection and podophyllin was shown
236 to be significantly more effective than podophyllin alone, as determined by the
237 number of patients whose lesions cleared. This significant difference in response
238 was evident after the second treatment (Week 3) and continued through 8 weeks
239 posttreatment. At the time of the patient's best response, 67% (33/49) of the
240 INTRON A and podophyllin treated patients had all three treated lesions clear while
241 42% (20/48) of the podophyllin treated patients had all three clear (p=0.003).

242

243 **AIDS-Related Kaposi's Sarcoma** The safety and efficacy of INTRON A in the
244 treatment of Kaposi's Sarcoma (KS), a common manifestation of the Acquired
245 Immune Deficiency Syndrome (AIDS), were evaluated in clinical trials in 144
246 patients.

247 In one study, INTRON A doses of 30 million IU/m² were administered
248 subcutaneously three times per week (TIW), to patients with AIDS-Related KS.
249 Doses were adjusted for patient tolerance. The average weekly dose delivered in
250 the first 4 weeks was 150 million IU; at the end of 12 weeks this averaged
251 110 million IU/week; and by 24 weeks averaged 75 million IU/week.

252 Forty-four percent of asymptomatic patients responded vs 7% of symptomatic
253 patients. The median time to response was approximately 2 months and 1 month,
254 respectively, for asymptomatic and symptomatic patients. The median duration of
255 response was approximately 3 months and 1 month, respectively, for the
256 asymptomatic and symptomatic patients. Baseline T4/T8 ratios were 0.46 for
257 responders vs 0.33 for nonresponders.

258 In another study, INTRON A doses of 35 million IU were administered
259 subcutaneously, daily (QD), for 12 weeks. Maintenance treatment, with every other
260 day dosing (QOD), was continued for up to 1 year in patients achieving antitumor
261 and antiviral responses. The median time to response was 2 months and the
262 median duration of response was 5 months in the asymptomatic patients.

263 In all studies, the likelihood of response was greatest in patients with
264 relatively intact immune systems as assessed by baseline CD4 counts
265 (interchangeable with T4 counts). Results at doses of 30 million IU/m² TIW and
266 35 million IU/QD, subcutaneously were similar and are provided together in
267 TABLE 1. This table demonstrates the relationship of response to baseline CD4
268 count in both asymptomatic and symptomatic patients in the 30 million IU/m² TIW
269 and the 35 million IU/QD treatment groups.

270 In the 30 million IU study group, 7% (5/72) of patients were complete
271 responders and 22% (16/72) of the patients were partial responders. The 35 million
272 IU study had 13% (3/23 patients) complete responders and 17% (4/23) partial
273 responders.

274 For patients who received 30 million IU TIW, the median survival time was
275 longer in patients with CD4 >200 (30.7 months) than in patients with CD4 ≤200
276 (8.9 months). Among responders, the median survival time was 22.6 months vs



277 9.7 months in nonresponders.

278

279 **Chronic Hepatitis C** The safety and efficacy of INTRON A in the treatment of
280 chronic hepatitis C was evaluated in 5 randomized clinical studies in which an
281 INTRON A dose of 3 million IU three times a week (TIW) was assessed. The initial
282 three studies were placebo-controlled trials that evaluated a 6-month (24-week)
283 course of therapy. In each of the three studies, INTRON A therapy resulted in a
284 reduction in serum alanine aminotransferase (ALT) in a greater proportion of
285 patients vs control patients at the end of 6 months of dosing. During the 6 months of
286 follow-up, approximately 50% of the patients who responded maintained their ALT
287 response. A combined analysis comparing pretreatment and posttreatment liver
288 biopsies revealed histological improvement in a statistically significantly greater
289 proportion of INTRON A treated patients compared to controls.

290 Two additional studies have investigated longer treatment durations (up to
291 24 months).^{5,6} Patients in the two studies to evaluate longer duration of treatment
292 had hepatitis with or without cirrhosis in the absence of decompensated liver
293 disease. Complete response to treatment was defined as normalization of the final
294 two serum ALT levels during the treatment period. A sustained response was
295 defined as a complete response at the end of the treatment period with sustained
296 normal ALT values lasting at least 6 months following discontinuation of therapy.

297 In Study 1, all patients were initially treated with INTRON A 3 million IU TIW
298 subcutaneously for 24 weeks (run-in period). Patients who completed the initial
299 24-week treatment period were then randomly assigned to receive no further
300 treatment, or to receive 3 million IU TIW for an additional 48 weeks. In Study 2,
301 patients who met the entry criteria were randomly assigned to receive INTRON A
302 3 million IU TIW subcutaneously for 24 weeks or to receive INTRON A 3 MIU TIW
303 subcutaneously for 96 weeks. In both studies, patient follow-up was variable and
304 some data collection was retrospective.

305 Results show that longer durations of INTRON A therapy improved the
306 sustained response rate (see **TABLE 2**). In patients with complete responses (CR)
307 to INTRON A therapy after 6 months of treatment (149/352 [42%]), responses were
308 less often sustained if drug was discontinued (21/70 [30%]) than if it was continued
309 for 18 to 24 months (44/79 [56%]). Of all patients randomized, the sustained
310 response rate in the patients receiving 18 or 24 months of therapy was 22% and
311 26%, respectively, in the two trials. In patients who did not have a CR by 6 months,
312 additional therapy did not result in significantly more responses, since almost all
313 patients who responded to therapy did so within the first 16 weeks of treatment.

314 A subset (<50%) of patients from the combined extended dosing studies had
315 liver biopsies performed both before and after INTRON A treatment. Improvement in
316 necroinflammatory activity as assessed retrospectively by the Knodell (Study 1) and
317 Scheuer (Study 2) Histology Activity Indices was observed in both studies. A higher
318 number of patients (58%, 45/78) improved with extended therapy than with shorter
319 (6 months) therapy (38%, 34/89) in this subset.

320 **REBETRON[®]** Combination Therapy containing INTRON A and **REBETOL[®]**
321 (ribavirin, USP) provided a significant reduction in virologic load and improved
322 histologic response in adult patients with compensated liver disease who were



323 treatment naïve or had relapsed following therapy with alfa interferon alone; pediatric
324 patients previously untreated with alfa interferon experienced a sustained virologic
325 response. See REBETRON Combination Therapy and REBETOL package inserts
326 for additional information.

327

328 **Chronic Hepatitis B Adults** The safety and efficacy of INTRON A in the treatment
329 of chronic hepatitis B were evaluated in three clinical trials in which INTRON A
330 doses of 30 to 35 million IU per week were administered subcutaneously (SC), as
331 either 5 million IU daily (QD), or 10 million IU three times a week (TIW) for 16 weeks
332 vs no treatment. All patients were 18 years of age or older with compensated liver
333 disease, and had chronic hepatitis B virus (HBV) infection (serum HBsAg positive for
334 at least 6 months) and HBV replication (serum HBeAg positive). Patients were also
335 serum HBV-DNA positive, an additional indicator of HBV replication, as measured by
336 a research assay.^{7,8} All patients had elevated serum alanine aminotransferase (ALT)
337 and liver biopsy findings compatible with the diagnosis of chronic hepatitis. Patients
338 with the presence of antibody to human immunodeficiency virus (anti-HIV) or
339 antibody to hepatitis delta virus (anti-HDV) in the serum were excluded from the
340 studies.

341 Virologic response to treatment was defined in these studies as a loss of
342 serum markers of HBV replication (HBeAg and HBV DNA). Secondary parameters
343 of response included loss of serum HBsAg, decreases in serum ALT, and
344 improvement in liver histology.

345 In each of two randomized controlled studies, a significantly greater
346 proportion of INTRON A treated patients exhibited a virologic response compared
347 with untreated control patients (see **TABLE 3**). In a third study without a concurrent
348 control group, a similar response rate to INTRON A therapy was observed.
349 Pretreatment with prednisone, evaluated in two of the studies, did not improve the
350 response rate and provided no additional benefit.

351 The response to INTRON A therapy was durable. No patient responding to
352 INTRON A therapy at a dose of 5 million IU QD or 10 million IU TIW, relapsed during
353 the follow-up period which ranged from 2 to 6 months after treatment ended. The
354 loss of serum HBeAg and HBV DNA was maintained in 100% of 19 responding
355 patients followed for 3.5 to 36 months after the end of therapy.

356 In a proportion of responding patients, loss of HBeAg was followed by the
357 loss of HBsAg. HBsAg was lost in 27% (4/15) of patients who responded to
358 INTRON A therapy at a dose of 5 million IU QD, and 35% (8/23) of patients who
359 responded to 10 million IU TIW. No untreated control patient lost HBsAg in these
360 studies.

361 In an ongoing study to assess the long-term durability of virologic response,
362 64 patients responding to INTRON A therapy have been followed for 1.1 to 6.6 years
363 after treatment; 95% (61/64) remain serum HBeAg negative and 49% (30/61) lost
364 serum HBsAg.

365 INTRON A therapy resulted in normalization of serum ALT in a significantly
366 greater proportion of treated patients compared to untreated patients in each of two
367 controlled studies (see **TABLE 4**). In a third study without a concurrent control



368 group, normalization of serum ALT was observed in 50% (12/24) of patients
369 receiving INTRON A therapy.

370 Virologic response was associated with a reduction in serum ALT to normal or
371 near normal (≤ 1.5 x the upper limit of normal) in 87% (13/15) of patients responding
372 to INTRON A therapy at 5 million IU QD, and 100% (23/23) of patients responding to
373 10 million IU TIW.

374 Improvement in liver histology was evaluated in Studies 1 and 3 by
375 comparison of pretreatment and 6 month posttreatment liver biopsies using the
376 semi-quantitative Knodell Histology Activity Index.⁹ No statistically significant
377 difference in liver histology was observed in treated patients compared to control
378 patients in Study 1. Although statistically significant histological improvement from
379 baseline was observed in treated patients in Study 3 ($p \leq 0.01$), there was no control
380 group for comparison. Of those patients exhibiting a virologic response following
381 treatment with 5 million IU QD or 10 million IU TIW, histological improvement was
382 observed in 85% (17/20) compared to 36% (9/25) of patients who were not virologic
383 responders. The histological improvement was due primarily to decreases in
384 severity of necrosis, degeneration, and inflammation in the periportal, lobular, and
385 portal regions of the liver (Knodell Categories I + II + III). Continued histological
386 improvement was observed in four responding patients who lost serum HBsAg and
387 were followed 2 to 4 years after the end of INTRON A therapy.¹⁰

388
389 **Pediatrics** The safety and efficacy of INTRON A in the treatment of chronic
390 hepatitis B was evaluated in one randomized controlled trial of 149 patients ranging
391 from 1 year to 17 years of age. Seventy-two patients were treated with 3 million
392 IU/m² of INTRON A therapy administered subcutaneously three times a week (TIW)
393 for 1 week; the dose was then escalated to 6 million IU/m² TIW for a minimum of 16
394 weeks up to 24 weeks. The maximum weekly dosage was 10 million IU TIW.
395 Seventy-seven patients were untreated controls. Study entry and response criteria
396 were identical to those described in the adult patient population.

397 Patients treated with INTRON A therapy had a better response (loss of HBV
398 DNA and HBeAg at 24 weeks of follow-up) compared to the untreated controls (24%
399 [17/72] vs 10% [8/77] $p=0.05$). Sixteen of the 17 responders treated with INTRON A
400 therapy remained HBV DNA and HBeAg negative and had a normal serum ALT 12
401 to 24 months after completion of treatment. Serum HBsAg became negative in 7 out
402 of 17 patients who responded to INTRON A therapy. None of the control patients
403 who had an HBV DNA and HBeAg response became HBsAg negative. At 24 weeks
404 of follow-up, normalization of serum ALT was similar in patients treated with
405 INTRON A therapy (17%, 12/72) and in untreated control patients (16%, 12/77).
406 Patients with a baseline HBV DNA < 100 pg/mL were more likely to respond to
407 INTRON A therapy than were patients with a baseline HBV DNA > 100 pg/mL (35%
408 vs 9%, respectively). Patients who contracted hepatitis B through maternal vertical
409 transmission had lower response rates than those who contracted the disease by
410 other means (5% vs 31%, respectively). There was no evidence that the effects on
411 HBV DNA and HBeAg were limited to specific subpopulations based on age, gender,
412 or race.



413

414

TABLE 1
RESPONSE BY BASELINE CD4 COUNT* IN AIDS-RELATED KS PATIENTS

	30 million IU/m ²			
	TIW, SC and 35 million IU QD, SC			
	Asymptomatic		Symptomatic	
CD4<200	4/14	(29%)	0/19	(0%)
200≤CD4≤400	6/12	(50%)	0/5	(0%)
CD4>400	5/7	(71%)	0/0	(0%)

* Data for CD4, and asymptomatic and symptomatic classification were not available for all patients.

415

TABLE 2
SUSTAINED ALT RESPONSE RATE VS DURATION OF THERAPY
IN CHRONIC HEPATITIS C PATIENTS
INTRON A 3 Million IU TIW

Study Number	Treatment Group* - Number of Patients (%)		Difference (Extended - 24 weeks) (95% CI) [‡]
	INTRON A 3 million IU 24 weeks of treatment	INTRON A 3 million IU 72 or 96 weeks of treatment [†]	
ALT response at the end of follow-up			
1	12/101 (12%)	23/104 (22%)	10% (-3, 24)
2	9/67 (13%)	21/80 (26%)	13% (-4, 30)
Combined Studies	21/168 (12.5%)	44/184 (24%)	11.4% (2, 21)
ALT response at the end of treatment			
1	40/101 (40%)	51/104 (49%)	--
2	32/67(48%)	35/80 (44%)	--

* Intent to treat groups.

† Study 1: 72 weeks of treatment; Study 2: 96 weeks of treatment.

‡ Confidence intervals adjusted for multiple comparisons due to 3 treatment arms in the study.

416

417

TABLE 3
VIROLOGIC RESPONSE* IN CHRONIC HEPATITIS B PATIENTS

Study Number	Treatment Group [†] - Number of Patients (%)				p [‡] Value
	INTRON A 5 million IU QD	INTRON A 10 million IU TIW	Untreated Controls		
1 ⁷	15/38 (39%)	--	3/42 (7%)		0.0009
2	--	10/24 (42%)	1/22 (5%)		0.005
3 ⁸	--	13/24 ^d (54%)	2/27 (7%) ^d		NA [§]
All Studies	15/38 (39%)	23/48 (48%)	6/91 (7%)		--

* Loss of HBeAg and HBV DNA by 6 months posttherapy.

† Patients pretreated with prednisone not shown.

‡ INTRON A treatment group vs untreated control.

§ Untreated control patients evaluated after 24-week observation period. A subgroup subsequently received INTRON A therapy. A direct comparison is not applicable (NA).

418



419

TABLE 4
ALT RESPONSES* IN CHRONIC HEPATITIS B PATIENTS

Study Number	Treatment Group - Number of Patients (%)						p [†] Value
	INTRON A 5 million IU QD		INTRON A 10 million IU TIW		Untreated Controls		
1	16/38	(42%)	--	--	8/42	(19%)	0.03
2	--	--	10/24	(42%)	1/22	(5%)	0.0034
3	--	--	12/24 ^c	(50%)	2/27	(7%) ^c	NA [‡]
All Studies	16/38	(42%)	22/48	(46%)	11/91	(12%)	--

* Reduction in serum ALT to normal by 6 months posttherapy.

† INTRON A treatment group vs untreated control.

‡ Untreated control patients evaluated after 24-week observation period. A subgroup subsequently received INTRON A therapy. A direct comparison is not applicable (NA).

420

421

INDICATIONS AND USAGE

422

Hairy Cell Leukemia INTRON A is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia.

423

424

425

Malignant Melanoma INTRON A is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence within 56 days of surgery.

426

427

428

429

Follicular Lymphoma INTRON A is indicated for the initial treatment of clinically aggressive (see **Clinical Experience**) follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older. Efficacy of INTRON A therapy in patients with low-grade, low-tumor burden follicular Non-Hodgkin's Lymphoma has not been demonstrated.

430

431

432

433

434

435

Condylomata Acuminata INTRON A is indicated for intralesional treatment of selected patients 18 years of age or older with condylomata acuminata involving external surfaces of the genital and perianal areas (see **DOSAGE AND ADMINISTRATION**).

436

437

438

439

The use of this product in adolescents has not been studied.

440

441

AIDS-Related Kaposi's Sarcoma INTRON A is indicated for the treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. The likelihood of response to INTRON A therapy is greater in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count.

442

443

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445

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447

Chronic Hepatitis C INTRON A is indicated for the treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease who have a history of blood or blood product exposure and/or are HCV antibody positive. Studies in these patients demonstrated that INTRON A therapy can produce clinically meaningful effects on this disease, manifested by normalization of serum alanine aminotransferase (ALT) and reduction in liver necrosis and degeneration.

448

449

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451

452



453 A liver biopsy should be performed to establish the diagnosis of chronic
 454 hepatitis. Patients should be tested for the presence of antibody to HCV. Patients
 455 with other causes of chronic hepatitis, including autoimmune hepatitis, should be
 456 excluded. Prior to initiation of INTRON A therapy, the physician should establish
 457 that the patient has compensated liver disease. The following patient entrance
 458 criteria for compensated liver disease were used in the clinical studies and should be
 459 considered before INTRON A treatment of patients with chronic hepatitis C:

- 460
- 461 • No history of hepatic encephalopathy, variceal bleeding, ascites, or other
 462 clinical signs of decompensation
 - 463 • Bilirubin ≤ 2 mg/dL
 - 464 • Albumin Stable and within normal limits
 - 465 • Prothrombin Time < 3 seconds prolonged
 - 466 • WBC $\geq 3000/\text{mm}^3$
 - 467 • Platelets $\geq 70,000/\text{mm}^3$

468
 469 Serum creatinine should be normal or near normal.

470 Prior to initiation of INTRON A therapy, CBC and platelet counts should be
 471 evaluated in order to establish baselines for monitoring potential toxicity. These tests
 472 should be repeated at weeks 1 and 2 following initiation of INTRON A therapy, and
 473 monthly thereafter. Serum ALT should be evaluated at approximately 3-month
 474 intervals to assess response to treatment (see **DOSAGE AND ADMINISTRATION**).

475 Patients with preexisting thyroid abnormalities may be treated if thyroid
 476 stimulating hormone (TSH) levels can be maintained in the normal range by
 477 medication. TSH levels must be within normal limits upon initiation of INTRON A
 478 treatment and TSH testing should be repeated at 3 and 6 months (see
 479 **PRECAUTIONS - Laboratory Tests**).

480 INTRON A in combination with REBETOL (ribavirin, USP) is indicated for the
 481 treatment of chronic hepatitis C in patients 3 years of age and older with
 482 compensated liver disease previously untreated with alfa interferon therapy and in
 483 patients 18 years of age and older who have relapsed following alfa interferon
 484 therapy. See REBETON Combination Therapy and REBETOL package inserts for
 485 additional information.

486
 487 **Chronic Hepatitis B** INTRON A is indicated for the treatment of chronic hepatitis B
 488 in patients 1 year of age or older with compensated liver disease. Patients who
 489 have been serum HBsAg positive for at least 6 months and have evidence of HBV
 490 replication (serum HBeAg positive) with elevated serum ALT are candidates for
 491 treatment. Studies in these patients demonstrated that INTRON A therapy can
 492 produce virologic remission of this disease (loss of serum HBeAg), and
 493 normalization of serum aminotransferases. INTRON A therapy resulted in the loss of
 494 serum HBsAg in some responding patients.



495 Prior to initiation of INTRON A therapy, it is recommended that a liver biopsy
 496 be performed to establish the presence of chronic hepatitis and the extent of liver
 497 damage. The physician should establish that the patient has compensated liver
 498 disease. The following patient entrance criteria for compensated liver disease were
 499 used in the clinical studies and should be considered before INTRON A treatment of
 500 patients with chronic hepatitis B:

- 501
- 502 • No history of hepatic encephalopathy, variceal bleeding, ascites, or other
 503 signs of clinical decompensation
 - 504 • Bilirubin Normal
 - 505 • Albumin Stable and within normal limits
 - 506 • Prothrombin Time *Adults* <3 seconds prolonged
 507 *Pediatrics* ≤2 seconds prolonged
 - 508 • WBC ≥4000/mm³
 - 509 • Platelets *Adults* ≥100,000/mm³
 510 *Pediatrics* ≥150,000/mm³

511

512 Patients with causes of chronic hepatitis other than chronic hepatitis B or
 513 chronic hepatitis C should not be treated with INTRON A Interferon alfa-2b,
 514 recombinant for Injection. CBC and platelet counts should be evaluated prior to
 515 initiation of INTRON A therapy in order to establish baselines for monitoring potential
 516 toxicity. These tests should be repeated at treatment Weeks 1, 2, 4, 8, 12, and 16.
 517 Liver function tests, including serum ALT, albumin and bilirubin, should be evaluated
 518 at treatment Weeks 1, 2, 4, 8, 12, and 16. HBeAg, HBsAg, and ALT should be
 519 evaluated at the end of therapy, as well as 3 and 6 months posttherapy, since
 520 patients may become virologic responders during the 6-month period following the
 521 end of treatment. In clinical studies in adults, 39% (15/38) of responding patients lost
 522 HBeAg 1 to 6 months following the end of INTRON A therapy. Of responding
 523 patients who lost HBsAg, 58% (7/12) did so 1-to-6 months posttreatment.

524 A transient increase in ALT ≥2 times baseline value (flare) can occur during
 525 INTRON A therapy for chronic hepatitis B. In clinical trials in adults and pediatrics,
 526 this flare generally occurred 8 to 12 weeks after initiation of therapy and was more
 527 frequent in responders (adults 63%, 24/38; pediatrics 59%, 10/17) than in
 528 nonresponders (adults 27%, 13/48; pediatrics 35%, 19/55). However, in adults and
 529 pediatrics, elevations in bilirubin ≥3 mg/dL (≥2 times ULN) occurred infrequently
 530 (adults 2%, 2/86; pediatrics 3%, 2/72) during therapy. When ALT flare occurs, in
 531 general, INTRON A therapy should be continued unless signs and symptoms of liver
 532 failure are observed. During ALT flare, clinical symptomatology and liver function
 533 tests including ALT, prothrombin time, alkaline phosphatase, albumin, and bilirubin,
 534 should be monitored at approximately 2-week intervals (see **WARNINGS**).

535
 536
 537

CONTRAINDICATIONS

INTRON A is contraindicated in patients with:



- 538 • Hypersensitivity to interferon alfa or any component of the product.
- 539 • Autoimmune hepatitis
- 540 • Decompensated liver disease

541

542 INTRON A and REBETOL (ribavirin, USP) combination therapy is additionally
543 contraindicated in:

544

- 545 • Patients with hypersensitivity to ribavirin or any other component of the
546 product
- 547 • Women who are pregnant
- 548 • Men whose female partners are pregnant
- 549 • Patients with hemoglobinopathies (e.g. thalassemia major, sickle cell anemia)

550

551 See REBETRON Combination Therapy package insert and REBETOL package
552 insert for additional information.

553

554 **WARNINGS**

555 **General** Moderate to severe adverse experiences may require modification of the
556 patient's dosage regimen or in some cases, termination of INTRON A therapy.
557 Because of the fever and other "flu-like" symptoms associated with INTRON A
558 administration, it should be used cautiously in patients with debilitating medical
559 conditions, such as those with a history of pulmonary disease (eg, chronic
560 obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution
561 should also be observed in patients with coagulation disorders (eg, thrombophlebitis,
562 pulmonary embolism) or severe myelosuppression.

563

564 **Cardiovascular Disorders**

565 INTRON A therapy should be used cautiously in patients with a history of
566 cardiovascular disease. Those patients with a history of myocardial infarction and/or
567 previous or current arrhythmic disorder who require INTRON A therapy should be
568 closely monitored (see **Laboratory Tests**). Cardiovascular adverse experiences,
569 which include hypotension, arrhythmia, or tachycardia of 150 beats per minute or
570 greater, and rarely cardiomyopathy and myocardial infarction, have been observed
571 in some INTRON A treated patients. Some patients with these adverse events had
572 no history of cardiovascular disease. Transient cardiomyopathy was reported in
573 approximately 2% of the AIDS-Related Kaposi's Sarcoma patients treated with
574 INTRON A Interferon alfa-2b, recombinant for Injection. Hypotension may occur
575 during INTRON A administration, or up to 2 days posttherapy, and may require
576 supportive therapy including fluid replacement to maintain intravascular volume.

577 Supraventricular arrhythmias occurred rarely and appeared to be correlated
578 with preexisting conditions and prior therapy with cardiotoxic agents. These adverse
579 experiences were controlled by modifying the dose or discontinuing treatment, but
580 may require specific additional therapy.

581

582 **Neuropsychiatric Disorders**



583 DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL
584 IDEATION, SUICIDAL ATTEMPTS, AND COMPLETED SUICIDES HAVE BEEN
585 REPORTED IN ASSOCIATION WITH TREATMENT WITH ALFA INTERFERONS,
586 INCLUDING INTRON A THERAPY. Patients with a preexisting psychiatric
587 condition, especially depression, or a history of severe psychiatric disorder should
588 not be treated with INTRON A.¹¹ INTRON A therapy should be discontinued for any
589 patient developing severe depression or other psychiatric disorder during treatment.
590 Obtundation and coma have also been observed in some patients, usually elderly,
591 treated at higher doses. While these effects are usually rapidly reversible upon
592 discontinuation of therapy, full resolution of symptoms has taken up to 3 weeks in a
593 few severe episodes. Narcotics, hypnotics, or sedatives may be used concurrently
594 with caution and patients should be closely monitored until the adverse effects have
595 resolved. Suicidal ideation or attempts occurred more frequently among pediatric
596 patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during
597 treatment and off therapy follow up.

598

599 **Bone marrow toxicity**

600 INTRON A therapy suppresses bone marrow function and may result in
601 severe cytopenias including very rare events of aplastic anemia. It is advised that
602 complete blood counts (CBC) be obtained pretreatment and monitored routinely
603 during therapy (see **PRECAUTIONS: Laboratory Tests**). INTRON A therapy
604 should be discontinued in patients who develop severe decreases in neutrophil (<0.5
605 $\times 10^9/L$) or platelet counts ($<25 \times 10^9/L$) (see **DOSAGE AND ADMINISTRATION:**
606 **Guidelines for Dose Modification**).

607

608 **Ophthalmologic Disorders**

609 Decrease or loss of vision, retinopathy including macular edema, retinal artery
610 or vein thrombosis, retinal hemorrhages and cotton wool spots; optic neuritis and
611 papilledema may be induced or aggravated by treatment with Interferon alfa-2b or
612 other alpha interferons. All patients should receive an eye examination at baseline.
613 Patients with pre-existing ophthalmologic disorders (eg, diabetic or hypertensive
614 retinopathy) should receive periodic ophthalmologic exams during interferon alpha
615 treatment. Any patient who develops ocular symptoms should receive a prompt and
616 complete eye examination. Interferon alfa-2b treatment should be discontinued in
617 patients who develop new or worsening ophthalmologic disorders.

618

619 **Endocrine Disorders**

620 Infrequently, patients receiving INTRON A therapy developed thyroid
621 abnormalities, either hypothyroid or hyperthyroid. The mechanism by which
622 INTRON A Interferon alfa-2b, recombinant for Injection may alter thyroid status is
623 unknown. Patients with preexisting thyroid abnormalities whose thyroid function
624 cannot be maintained in the normal range by medication should not be treated with
625 INTRON A. Prior to initiation of INTRON A therapy, serum TSH should be
626 evaluated. Patients developing symptoms consistent with possible thyroid
627 dysfunction during the course of INTRON A therapy should have their thyroid
628 function evaluated and appropriate treatment instituted. Therapy should be



629 discontinued for patients developing thyroid abnormalities during treatment whose
630 thyroid function cannot be normalized by medication. Discontinuation of INTRON A
631 therapy has not always reversed thyroid dysfunction occurring during treatment.
632 Diabetes mellitus has been observed in patients treated with alpha interferons.
633 Patients with these conditions who cannot be effectively treated by medication
634 should not begin INTRON A therapy. Patients who develop these conditions during
635 treatment and cannot be controlled with medication should not continue INTRON A
636 therapy.

637

638 **Gastrointestinal Disorders**

639 Hepatotoxicity, including fatality, has been observed in interferon alfa treated
640 patients, including those treated with INTRON A. Any patient developing liver
641 function abnormalities during treatment should be monitored closely and if
642 appropriate, treatment should be discontinued.

643

644 **Pulmonary Disorders**

645 Pulmonary infiltrates, pneumonitis and pneumonia, including fatality, have
646 been observed in interferon alfa treated patients, including those treated with
647 INTRON A. The etiologic explanation for these pulmonary findings has yet to be
648 established. Any patient developing fever, cough, dyspnea, or other respiratory
649 symptoms should have a chest X-ray taken. If the chest X-ray shows pulmonary
650 infiltrates or there is evidence of pulmonary function impairment, the patient should
651 be closely monitored and, if appropriate, interferon alfa treatment should be
652 discontinued. While this has been reported more often in patients with chronic
653 hepatitis C treated with interferon alfa, it has also been reported in patients with
654 oncologic diseases treated with interferon alfa.

655

656 **Autoimmune Disorders**

657 Rare cases of autoimmune diseases including thrombocytopenia, vasculitis,
658 Raynaud's phenomenon, rheumatoid arthritis, lupus erythematosus, and
659 rhabdomyolysis have been observed in patients treated with alfa interferons,
660 including patients treated with INTRON A. In very rare cases the event resulted in
661 fatality. The mechanism by which these events developed and their relationship to
662 interferon alfa therapy is not clear. Any patient developing an autoimmune disorder
663 during treatment should be closely monitored and, if appropriate, treatment should
664 be discontinued.

665

666 **Human Albumin** The powder formulations of this product contain albumin, a
667 derivative of human blood. Based on effective donor screening and product
668 manufacturing processes, it carries an extremely remote risk for transmission of viral
669 diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also
670 is considered extremely remote. No cases of transmission of viral diseases or CJD
671 have ever been identified for albumin.

672

673 **AIDS-Related Kaposi's Sarcoma** INTRON A therapy should not be used for
674 patients with rapidly progressive visceral disease (see **CLINICAL**



675 **PHARMACOLOGY**). Also of note, there may be synergistic adverse effects
676 between INTRON A and zidovudine. Patients receiving concomitant zidovudine
677 have had a higher incidence of neutropenia than that expected with zidovudine
678 alone. Careful monitoring of the WBC count is indicated in all patients who are
679 myelosuppressed and in all patients receiving other myelosuppressive medications.
680 The effects of INTRON A when combined with other drugs used in the treatment of
681 AIDS-Related disease are unknown.

682

683 **Chronic Hepatitis C and Chronic Hepatitis B** Patients with decompensated liver
684 disease, autoimmune hepatitis or a history of autoimmune disease, and patients who
685 are immunosuppressed transplant recipients should not be treated with INTRON A.
686 There are reports of worsening liver disease, including jaundice, hepatic
687 encephalopathy, hepatic failure, and death following INTRON A therapy in such
688 patients. Therapy should be discontinued for any patient developing signs and
689 symptoms of liver failure.

690 Chronic hepatitis B patients with evidence of decreasing hepatic synthetic
691 functions, such as decreasing albumin levels or prolongation of prothrombin time,
692 who nevertheless meet the entry criteria to start therapy, may be at increased risk of
693 clinical decompensation if a flare of aminotransferases occurs during INTRON A
694 treatment. In such patients, if increases in ALT occur during INTRON A therapy for
695 chronic hepatitis B, they should be followed carefully including close monitoring of
696 clinical symptomatology and liver function tests, including ALT, prothrombin time,
697 alkaline phosphatase, albumin, and bilirubin. In considering these patients for
698 INTRON A therapy, the potential risks must be evaluated against the potential
699 benefits of treatment.

700

701 **Use with Ribavirin** (See also **REBETRON** and **REBETOL** Package Inserts)
702 REBETOL may cause birth defects and/or death of the unborn child. REBETOL
703 therapy should not be started until a report of a negative pregnancy test has been
704 obtained immediately prior to planned initiation of therapy. Patients should use at
705 least two forms of contraception and have monthly pregnancy tests (See
706 **CONTRAINDICATIONS** and **PRECAUTIONS**: Information for Patients).

707

708 Combination Therapy containing INTRON A and REBETOL (ribavirin, USP) was
709 associated with hemolytic anemia. Hemoglobin <10 g/dL was observed in
710 approximately 10% of adult and pediatric patients in clinical trials. Anemia occurred
711 within 1 to 2 weeks of initiation of ribavirin therapy. Combination Therapy containing
712 INTRON A and REBETOL (ribavirin, USP) should **not** be used in patients with
713 creatinine clearance <50 mL/min. See REBETRON Combination Therapy and or
714 REBETOL package inserts for additional information.

715

716 **PRECAUTIONS**

717 **General** Acute serious hypersensitivity reactions (eg, urticaria, angioedema,
718 bronchoconstriction, anaphylaxis) have been observed rarely in INTRON A treated
719 patients; if such an acute reaction develops, the drug should be discontinued
720 immediately and appropriate medical therapy instituted. Transient rashes have



721 occurred in some patients following injection, but have not necessitated treatment
722 interruption.

723 While fever may be related to the flu-like syndrome reported commonly in
724 patients treated with interferon, other causes of persistent fever should be ruled out.

725 There have been reports of interferon, including INTRON A, exacerbating
726 preexisting psoriasis and sarcoidosis as well as development of new sarcoidosis.
727 Therefore, INTRON A therapy should be used in these patients only if the potential
728 benefit justifies the potential risk.

729 Variations in dosage, routes of administration, and adverse reactions exist
730 among different brands of interferon. Therefore, do not use different brands of
731 interferon in any single treatment regimen.

732 **Triglycerides** Elevated triglyceride levels have been observed in patients
733 treated with interferons including INTRON A therapy. Elevated triglyceride levels
734 should be managed as clinically appropriate. Hypertriglyceridemia may result in
735 pancreatitis. Discontinuation of INTRON A therapy should be considered for
736 patients with persistently elevated triglycerides (eg, triglycerides >1000 mg/dL)
737 associated with symptoms of potential pancreatitis, such as abdominal pain, nausea,
738 or vomiting.

739
740 **Drug Interactions** Interactions between INTRON A and other drugs have not been
741 fully evaluated. Caution should be exercised when administering INTRON A therapy
742 in combination with other potentially myelosuppressive agents such as zidovudine.
743 Concomitant use of alfa interferon and theophylline decreases theophylline
744 clearance resulting in a 100% increase in serum theophylline levels.

745
746 **Information for Patients** Patients receiving INTRON A alone or in combination with
747 REBETOL should be informed of the risks and benefits associated with treatment
748 and should be instructed on proper use of the product. To supplement your
749 discussion with a patient, you may wish to provide patients with a copy of the
750 **Medication Guide**.

751
752 Patients should be informed of, and advised to seek medical attention for symptoms
753 indicative of serious adverse reactions associated with this product. Such adverse
754 reactions may include depression (suicidal ideation), cardiovascular (chest pain),
755 ophthalmologic toxicity (decrease in/or loss of vision), pancreatitis or colitis (severe
756 abdominal pain) and cytopenias (high persistent fevers, bruising, dyspnea). Patients
757 should be advised that some side effects such as fatigue and decreased
758 concentration might interfere with the ability to perform certain tasks. Patients who
759 are taking INTRON A in combination with REBETOL must be thoroughly informed of
760 the risks to a fetus. Female patients and female partners of male patients must be
761 told to use two forms of birth control during treatment and for six months after
762 therapy is discontinued.(see **MEDICATION GUIDE**).

763 Patients should be advised to remain well hydrated during the initial stages of
764 treatment and that use of an antipyretic may ameliorate some of the flu-like
765 symptoms.

766



767 If a decision is made to allow a patient to self-administer INTRON A, a puncture
768 resistant container for the disposal of needles and syringes should be supplied.
769 Patients self-administering INTRON A should be instructed on the proper disposal of
770 needles and syringes and cautioned against reuse.

771 **Laboratory Tests** In addition to those tests normally required for monitoring
772 patients, the following laboratory tests are recommended for all patients on INTRON
773 A therapy, prior to beginning treatment and then periodically thereafter.

774

775 • Standard hematologic tests - including hemoglobin, complete and
776 differential white blood cell counts, and platelet count

777 • Blood chemistries - electrolytes, liver function tests, and TSH

778

779 Those patients who have preexisting cardiac abnormalities and/or are in
780 advanced stages of cancer should have electrocardiograms taken prior to and
781 during the course of treatment.

782 Mild to moderate leukopenia and elevated serum liver enzyme (SGOT) levels
783 have been reported with intralesional administration of INTRON A (see **ADVERSE**
784 **REACTIONS**); therefore, the monitoring of these laboratory parameters should be
785 considered.

786 Baseline chest x-rays are suggested and should be repeated if clinically
787 indicated.

788 For malignant melanoma patients, WBC count and liver function tests should
789 be monitored weekly during the induction phase of therapy and monthly during the
790 maintenance phase of therapy.

791 For specific recommendations in chronic hepatitis C and chronic hepatitis B,
792 see **INDICATIONS AND USAGE**.

793

794 **Carcinogenesis, Mutagenesis, Impairment of Fertility** Studies with INTRON A
795 have not been performed to determine carcinogenicity.

796 Interferon may impair fertility. In studies of interferon administration in
797 nonhuman primates, menstrual cycle abnormalities have been observed.
798 Decreases in serum estradiol and progesterone concentrations have been reported
799 in women treated with human leukocyte interferon.¹² Therefore, fertile women should
800 not receive INTRON A therapy unless they are using effective contraception during
801 the therapy period. INTRON A therapy should be used with caution in fertile men.

802 Mutagenicity studies have demonstrated that INTRON A Interferon alfa-2b,
803 recombinant for Injection is not mutagenic.

804 Studies in mice (0.1, 1.0 million IU/day), rats (4, 20, 100 million IU/kg/day),
805 and cynomolgus monkeys (1.1 million IU/kg/day; 0.25, 0.75, 2.5 million IU/kg/day)
806 injected with INTRON A for up to 9 days, 3 months, and 1 month, respectively, have
807 revealed no evidence of toxicity. However, in cynomolgus monkeys (4, 20, 100
808 million IU/kg/day) injected daily for 3 months with INTRON A toxicity was observed
809 at the mid and high doses and mortality was observed at the high dose.

810 However, due to the known species-specificity of interferon, the effects in
811 animals are unlikely to be predictive of those in man.



812 INTRON A in combination with REBETOL (ribavirin, USP) should be used
813 with caution in fertile men. See the REBETRON and REBETOL package inserts for
814 additional information.

815

816 **Pregnancy Category C** INTRON A has been shown to have abortifacient effects in
817 *Macaca mulatta* (rhesus monkeys) at 15 and 30 million IU/kg (estimated human
818 equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a
819 60-kg adult). There are no adequate and well-controlled studies in pregnant women.
820 INTRON A therapy should be used during pregnancy only if the potential benefit
821 justifies the potential risk to the fetus.

822

823 **Pregnancy Category X** applies to Combination Therapy with INTRON A
824 and REBETOL (ribavirin, USP) (see **CONTRAINDICATIONS**). See the
825 REBETRON Combination Therapy and REBETOL package inserts for additional
826 information. Significant teratogenic and/or embryocidal effects have been
827 demonstrated in all animal species exposed to ribavirin. REBETOL therapy is
828 contraindicated in women who are pregnant. See **CONTRAINDICATIONS** and the
829 REBETRON and REBETOL package inserts. If pregnancy occurs in a patient or
830 partner of a patient during treatment with INTRON A and REBETOL and during the 6
831 months after treatment cessation, physicians should report such cases by calling
832 (800) 593-2214.

833

834 **Nursing Mothers** It is not known whether this drug is excreted in human milk.
835 However, studies in mice have shown that mouse interferons are excreted into the
836 milk. Because of the potential for serious adverse reactions from the drug in nursing
837 infants, a decision should be made whether to discontinue nursing or to discontinue
838 INTRON A therapy, taking into account the importance of the drug to the mother.

839

840 **Pediatric Use** *General Safety* and effectiveness in pediatric patients have not been
841 established for indications other than chronic hepatitis B and chronic hepatitis C.
842 *Chronic Hepatitis B* Safety and effectiveness in pediatric patients ranging in age
843 from 1 to 17 years have been established based upon one controlled clinical trial
844 (see **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, DOSAGE AND**
845 **ADMINISTRATION; Chronic Hepatitis B**).

846

847 **Chronic Hepatitis C**

848 Safety and effectiveness in pediatric patients ranging in age from 3 to 16 years have
849 been established based upon clinical studies in 118 patients. See REBETOL
850 package insert for additional information. Suicidal ideation or attempts occurred
851 more frequently among pediatric patients compared to adults patients (2.4% versus
852 1%) during treatment and off-therapy follow-up (See **WARNINGS-Neuropsychiatric**
853 **Disorders**). During a 48-week course of therapy there was a decrease in the rate of
854 linear growth (mean percentile assignment decrease of 7%) and a decrease in the
855 rate of weight gain (mean percentile assignment decrease of 9%). A general
856 reversal of these trends was noted during the 24-week post-treatment period.

857



858

859 **ADVERSE REACTIONS**

860 **General** The adverse experiences listed below were reported to be possibly or
861 probably related to INTRON A therapy during clinical trials. Most of these adverse
862 reactions were mild to moderate in severity and were manageable. Some were
863 transient and most diminished with continued therapy.

864 The most frequently reported adverse reactions were "flu-like" symptoms,
865 particularly fever, headache, chills, myalgia, and fatigue. More severe toxicities are
866 observed generally at higher doses and may be difficult for patients to tolerate.

867 In addition, the following spontaneous adverse experiences have been
868 reported during the marketing surveillance of INTRON A: nephrotic syndrome,
869 pancreatitis, psychosis including hallucinations, renal failure, and renal insufficiency.
870 Very rarely, INTRON A used alone or in combination with REBETOL (ribavirin, USP)
871 may be associated with aplastic anemia. Rarely sarcoidosis or exacerbation of
872 sarcoidosis has been reported.



Treatment-Related Adverse Experiences By Indication								
Dosing Regimens								
Percentage (%) of Patients*								
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSI'S SARCOMA	CHRONIC HEPATITIS C ^{II}		
	20 MIU/m ² Induction (IV) 10 MIU/m ² Maintenance (SC)	5 MIU TIW/SC	2 MIU/m ² TIW/SC	1 MIU/lesion	30 MIU/m ² TIW/SC	35 MIU QD/SC	3 MIU TIW	5 MIU QD
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=183
Application-Site Disorders			20				5	3
injection site inflammation	--	1	--	--	--	--	5	3
other (≤5%)	burning, injection site bleeding, injection site pain, injection site reaction (5% in chronic hepatitis B pediatrics), itching							
Blood Disorders (<5%)	anemia, anemia hypochromic, granulocytopenia, hemolytic anemia, leukopenia, lymphocytosis, neutropenia (9% in chronic hepatitis B pediatrics), thrombocytopenia (10% in chronic hepatitis C) (bleeding 8% in malignant melanoma), thrombocytopenia							
Body as a Whole								
facial edema	--	1	--	<1	--	10	<1	3
weight decrease	3	13	<1	<1	5	3	10	2
other (≤5%)	allergic reaction, cachexia, dehydration, earache, hernia, edema, hypercalcemia, hyperglycemia, hypothermia, inflammation, lymphadenopathy, mastitis, periorbital edema, poor peripheral circulation, peripheral edema (6% in follicular lymphoma), phlebitis, scrotal/penile edema, thirst, weakness, weight increase							
Cardiovascular System Disorders (<5%)	angina, arrhythmia, atrial fibrillation, bradycardia, cardiac failure, cardiomegaly, cardiomyopathy, coronary artery disorder, extracranial hemorrhage, hematoma, hypertension (9% in chronic hepatitis C), hypotension, palpitations, phlebitis, postural hypotension, pulmonary embolism, tachycardia, thrombosis, varicose vein							
Endocrine System Disorders (<5%)	aggravation of diabetes mellitus, goiter, gynecomastia, hyperglycemia, hyperthyroidism, hypertriglyceridemia, hypothyroidism, hypoparathyroidism							
Flu-like Symptoms								
fever	81	56	68	56	47	55	34	6
headache	62	21	39	47	36	21	43	6
chills	54	--	46	45	--	--	--	--
myalgia	75	16	39	44	34	28	43	5
fatigue	96	8	61	18	84	48	23	7
increased sweating	6	13	8	2	4	21	4	1
asthenia	--	63	7	--	11	--	40	5
rigors	2	7	--	--	30	14	16	3
arthralgia	6	8	8	9	--	3	16	1
dizziness	23	--	12	9	7	24	9	1
influenza-like symptoms	10	18	37	--	45	79	26	5
back pain	--	15	19	6	1	3	--	--



Treatment-Related Adverse Experiences By Indication

ADVERSE EXPERIENCE	Dosing Regimens Percentage (%) of Patients*													
	MALIGNANT MELANOMA		FOLLICULAR LYMPHOMA		HAIRY CELL LEUKEMIA		CONDYLOMATO ACUMINATA		AIDS-RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C ^{II}		CHRONIC HEPATITIS B	
	20 MIU/m ² Induction (IV)	5 MIU TIW/SC	2 MIU/m ² TIW/SC	1 MIU/lesion	30 MIU/m ² TIW/SC	MIU QD/SC	MIU QD	MIU QD	MIU QD	MIU QD	MIU QD	MIU QD	MIU QD	MIU QD
	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116				
dry mouth	1	2	19	--	22	28	5	6	5-	--				
chest pain	2	8	<1	<1	1	28	4	4	--	--				
malaise	6	--	--	14	5	--	13	9	6	3				
pain (unspecified)	15	9	18	3	3	3	--	--	--	--				
other (<5%)														
	chest pain substernal, hyperthermia, rhinitis, rhinorrhea													
Gastrointestinal System Disorders														
diarrhea	35	19	18	2	18	45	13	19	8	12				
anorexia	69	21	19	1	38	41	14	43	53	43				
nausea	66	24	21	17	28	21	19	50	33	18				
taste alteration	24	2	13	<1	5	7	2	10	--	--				
abdominal pain	2	20	<5	1	5	21	16	5	4	23				
loose stools	--	1	--	<1	--	10	2	2	--	2				
vomiting	1	32	6	2	11	14	8	7	10	27				
constipation	1	14	<1	--	1	10	4	5	--	2				
gingivitis	2 [†]	7 [†]	--	--	--	14	--	1	--	--				
dyspepsia	--	2	--	2	4	--	7	3	8	3				
other (<5%)														
	abdominal ascites, abdominal distension, colitis, dysphagia, eructation, esophagitis, flatulence, gallstones, gastric ulcer, gastritis, gastroenteritis, gastrointestinal disorder (7% in follicular lymphoma), gastrointestinal hemorrhage, gastrointestinal mucosal discoloration, gingival bleeding, gum hyperplasia, halitosis, hemorrhoids, increased appetite, increased saliva, intestinal disorder, melena, mouth ulceration, mucositis, oral hemorrhage, oral leukoplakia, rectal bleeding after stool, rectal hemorrhage, stomatitis, stomatitis ulcerative, taste loss, tongue disorder, tooth disorder													
Liver and Biliary System Disorders (<5%)														
	abnormal hepatic function tests, biliary pain, bilirubinemia, hepatitis, increased lactate dehydrogenase, increased transaminases (SGOT/SGPT) (elevated SGOT 63% in malignant melanoma and 24% in follicular lymphoma), jaundice, right upper quadrant pain (15% in chronic hepatitis C), and very rarely, hepatic encephalopathy, hepatic failure, and death													
Musculoskeletal System Disorders														
musculoskeletal pain	--	18	--	--	--	--	21	9	1	10				
Other (<5%)														
	arthritis, arthritis aggravated, arthrosis, bone disorder, bone pain, carpal tunnel syndrome, hyporeflexia, leg cramps, muscle atrophy, muscle weakness, polyarthritis nodosa, tendinitis, rheumatoid arthritis, spondylitis													
Nervous System and														



Treatment-Related Adverse Experiences By Indication

ADVERSE EXPERIENCE	Dosing Regimens Percentage (%) of Patients*													
	MALIGNANT MELANOMA		FOLLICULAR LYMPHOMA		HAIRY CELL LEUKEMIA		CONDYLOMATA ACUMINATA		AIDS-RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C ^{††}		CHRONIC HEPATITIS B	
	N=143	N=135	N=145	N=74	N=29	N=183	N=101	N=78	N=116	Adults	Pediatrics			
20 MIU/m ²														
Induction (IV)	6	13	<1	--	31	1	4	--	5					
10 MIU/m ²	2	8	<5	1	31	3	7	1	7					
Maintenance (SC)	1	4	--	--	21	2	--	--	--					
	2	7	--	--	14	0	1	0	--					
	1	7	--	1	10	<1	4	<1	--					
other (<5%)														

Skin and Appendages Disorders

dermatitis	1	--	8	--	--	2	1	--	--
alopecia	29	23	8	--	31	28	26	38	17
pruritus	--	10	11	1	--	9	6	4	3
rash	19	13	25	--	10	5	8	1	5
dry skin	1	3	9	--	10	4	3	--	<1
other (<5%)									

abnormal hair texture, acne, cellulitis, cyanosis of the hand, cold and clammy skin, dermatitis lichenoides, eczema, epidermal necrolysis, erythema, erythema nodosum, folliculitis, furunculosis, increased hair growth, lacrimal gland disorder, lacrimation, lipoma, maculopapular rash, melanosis, nail disorders, nontherapeutic cold sores; pallor, peripheral ischemia, photosensitivity, pruritus genital, psoriasis, psoriasis aggravated, purpura (5% in chronic hepatitis C), rash erythematous, sebaceous cyst, skin depigmentation, skin discoloration, skin nodule, urticaria, vitiligo

albumin/protein in urine, cystitis, dysuria, hematuria, incontinence, increased BUN, micturition disorder, micturition frequency, nocturia, polyuria (10% in follicular lymphoma), renal insufficiency, urinary tract infection (5% in chronic hepatitis C)

abnormal vision, blurred vision, diplopia, dry eyes, eye pain, nystagmus, photophobia

- * Dash (--) indicates not reported
- † Vomiting was reported with nausea as a single term
- ‡ Includes stomatitis/mucositis
- § Amnesia was reported with confusion as a single term
- || Percentages based upon a summary of all adverse events during 18 to 24 months of treatment
- †† Predominantly lethargy



Hairy Cell Leukemia The adverse reactions most frequently reported during clinical trials in 145 patients with hairy cell leukemia were the "flu-like" symptoms of fever (68%), fatigue (61%), and chills (46%).

Malignant Melanoma The INTRON A dose was modified because of adverse events in 65% (n=93) of the patients. INTRON A therapy was discontinued because of adverse events in 8% of the patients during induction and 18% of the patients during maintenance. The most frequently reported adverse reaction was fatigue which was observed in 96% of patients. Other adverse reactions that were recorded in >20% of INTRON A treated patients included neutropenia (92%), fever (81%) myalgia (75%), anorexia (69%), vomiting/nausea (66%), increased SGOT (63%), headache (62%), chills (54%), depression (40%), diarrhea (35%), alopecia (29%), altered taste sensation (24%), dizziness/vertigo (23%), and anemia (22%).

Adverse reactions classified as severe or life-threatening (ECOG Toxicity Criteria grade 3 or 4) were recorded in 66% and 14% of INTRON A treated patients, respectively. Severe adverse reactions recorded in >10% of INTRON A treated patients included neutropenia/leukopenia (26%), fatigue (23%), fever (18%), myalgia (17%), headache (17%), chills (16%), and increased SGOT (14%). Grade 4 fatigue was recorded in 4% and grade 4 depression was recorded in 2% of INTRON A treated patients. No other grade 4 AE was reported in more than 2 INTRON A treated patients. Lethal hepatotoxicity occurred in 2 INTRON A treated patients early in the clinical trial. No subsequent lethal hepatotoxicity were observed with adequate monitoring of liver function tests (see **PRECAUTIONS - Laboratory Tests**).

Follicular Lymphoma Ninety-six percent of patients treated with CHVP plus INTRON A therapy and 91% of patients treated with CHVP alone reported an adverse event of any severity. Asthenia, fever, neutropenia, increased hepatic enzymes, alopecia, headache, anorexia, "flu-like" symptoms, myalgia, dyspnea, thrombocytopenia, paresthesia, and polyuria occurred more frequently in the CHVP plus INTRON A treated patients than in patients treated with CHVP alone. Adverse reactions classified as severe or life threatening (World Health Organization grade 3 or 4) recorded in >5% of CHVP plus INTRON A treated patients included neutropenia (34%), asthenia (10%), and vomiting (10%). The incidence of neutropenic infection was 6% in CHVP plus INTRON A vs 2% in CHVP alone. One patient in each treatment group required hospitalization.

Twenty-eight percent of CHVP plus INTRON A treated patients had a

intolerable asthenia (5/135), severe flu symptoms (2/135), and one patient each with exacerbation of ankylosing spondylitis, psychosis, and decreased ejection fraction.

Condylomata Acuminata Eighty-eight percent (311/352) of patients treated with INTRON A Interferon alfa-2b, recombinant for Injection for condylomata acuminata who were evaluable for safety, reported an adverse reaction during treatment. The incidence of the adverse reactions reported increased when the number of treated lesions increased from one to five. All 40 patients who had five warts treated, reported some type of adverse reaction during treatment.

Adverse reactions and abnormal laboratory test values reported by patients who were retreated were qualitatively and quantitatively similar to those reported during the initial INTRON A treatment period.

AIDS-Related Kaposi's Sarcoma In patients with AIDS-Related Kaposi's Sarcoma, some type of adverse reaction occurred in 100% of the 74 patients treated with 30 million IU/m² three times a week and in 97% of the 29 patients treated with 35 million IU per day.

Of these adverse reactions, those classified as severe (World Health Organization grade 3 or 4) were reported in 27% to 55% of patients. Severe adverse reactions in the 30 million IU/m² TIW study included: fatigue (20%), influenza-like symptoms (15%), anorexia (12%), dry mouth (4%), headache (4%), confusion (3%), fever (3%), myalgia (3%), and nausea and vomiting (1% each). Severe adverse reactions for patients who received the 35 million IU QD included: fever (24%), fatigue (17%), influenza-like symptoms (14%), dyspnea (14%), headache (10%), pharyngitis (7%), and ataxia, confusion, dysphagia, GI hemorrhage, abnormal hepatic function, increased SGOT, myalgia, cardiomyopathy, face edema, depression, emotional lability, suicide attempt, chest pain, and coughing (1 patient each). Overall, the incidence of severe toxicity was higher among patients who received the 35 million IU per day dose.

Chronic Hepatitis C Two studies of extended treatment (18 to 24 months) with INTRON A Interferon alfa-2b, recombinant for Injection show that approximately 95% of all patients treated experience some type of adverse event and that patients treated for extended duration continue to experience adverse events throughout treatment. Most adverse events reported are mild to moderate in severity. However, 29/152 (19%) of patients treated for 18 to 24 months experienced a serious adverse event compared to 11/163 (7%) of those treated for 6 months. Adverse events which occur or persist during extended treatment are similar in type and severity to those occurring during short-course therapy.

Of the patients achieving a complete response after 6 months of therapy, 12/79 (15%) subsequently discontinued INTRON A treatment during extended therapy because of adverse events, and 23/79 (29%) experienced severe adverse events (WHO grade 3 or 4) during extended therapy.

In patients using REBETRON Combination Therapy containing INTRON A and REBETOL (ribavirin, USP) Capsules, the primary toxicity observed was hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2



weeks of therapy. Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients treated with INTRON A/REBETOL therapy. See REBETRON Combination Therapy package insert for additional information.

Chronic Hepatitis B Adults In patients with chronic hepatitis B, some type of adverse reaction occurred in 98% of the 101 patients treated at 5 million IU QD and 90% of the 78 patients treated at 10 million IU TIW. Most of these adverse reactions were mild to moderate in severity, were manageable, and were reversible following the end of therapy.

Adverse reactions classified as severe (causing a significant interference with normal daily activities or clinical state) were reported in 21% to 44% of patients. The severe adverse reactions reported most frequently were the "flu-like" symptoms of fever (28%), fatigue (15%), headache (5%), myalgia (4%), rigors (4%), and other severe "flu-like" symptoms which occurred in 1% to 3% of patients. Other severe adverse reactions occurring in more than one patient were alopecia (8%), anorexia (6%), depression (3%), nausea (3%), and vomiting (2%).

To manage side effects, the dose was reduced or INTRON A therapy was interrupted in 25% to 38% of patients. Five percent of patients discontinued treatment due to adverse experiences.

Pediatrics In pediatric patients the most frequently reported adverse events were those commonly associated with interferon treatment; flu-like symptoms (100%), gastrointestinal system disorders (46%), and nausea and vomiting (40%). Neutropenia (13%) and thrombocytopenia (3%) were also reported. None of the adverse events were life threatening. The majority were moderate to severe and resolved upon dose reduction or drug discontinuation.



Abnormal Laboratory Test Values by Indication.

LABORATORY TESTS	Dosing Regimens Percentage (%) of Patients							
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSI'S SARCOMA	CHRONIC HEPATITIS C		
	20 MIU/m ² Induction (IV) 10 MIU/m ² Maintenance (SC)	5 MIU TIW/SC	2 MIU/m ² TIW/SC	1 MIU/lesion	30 MIU/m ² TIW/SC	35 MIU QD/SC	3 MIU TIW	5 MIU QD
	N=143	N=135	N=145	N=352	N=69-73	N=26-28	N=140-171	N=96-100
Hemoglobin	22	8	NA	--	1	15	26 [†]	32 [†]
White Blood Cell Count	"	--	NA	17	10	22	26 [†]	68 [†]
Platelet Count	15	13	NA	--	0	8	15 [‡]	12 [‡]
Serum Creatinine	3	2	0	--	--	--	6	3
Alkaline Phosphatase	13	--	4	--	--	--	--	8
Lactate Dehydrogenase	1	--	0	--	--	--	--	--
Serum Urea Nitrogen	12	4	0	--	--	--	--	2
SGOT	63	24	4	12	11	41	--	--
SGPT	2	--	13	--	10	15	--	--
Granulocyte Count								
• Total	92	36	NA	--	31	39	45 [§]	75 [§]
• 1000-<1500/mm ³	66	--	--	--	--	--	32	30
• 750-<1000/mm ³	--	21	--	--	--	--	10	24
• 500-<750/mm ³	25	--	--	--	--	--	1	17
• <500/mm ³	1	13	--	--	--	--	2	4

NA - Not Applicable- Patients' initial hematologic laboratory test values were abnormal due to their condition.

* Decrease of ≥ 2 g/dL.

** Decrease of ≥ 2 g/dL; 14% 2-<3 g/dL; 3% ≥ 3 g/dL.

† Decrease to $< 3000/\text{mm}^3$.

‡ Decrease to $< 70,000/\text{mm}^3$.

§ Neutrophils plus bands.

" White Blood Cell Count was reported as neutropenia.

†† Decrease of ≥ 2 g/dL; 20% 2-<3 g/dL; 6% ≥ 3 g/dL.



OVERDOSAGE

There is limited experience with overdosage. Postmarketing surveillance includes reports of patients receiving a single dose as great as 10 times the recommended dose. In general, the primary effects of an overdose are consistent with the effects seen with therapeutic doses of interferon alfa-2b. Hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with single administration overdoses and/or with longer durations of treatment than prescribed (see **ADVERSE REACTIONS**). Toxic effects after ingestion of interferon alfa-2b are not expected because interferons are poorly absorbed orally. Consultation with a poison center is recommended.

Treatment. There is no specific antidote for interferon alfa-2b. Hemodialysis and peritoneal dialysis are not considered effective for treatment of overdose.

DOSAGE AND ADMINISTRATION

General

IMPORTANT: INTRON A is supplied as 1) Powder for Injection/Reconstitution; 2) Solution for Injection in Vials; 3) Solution for Injection in Multidose Pens. **Not all dosage forms and strengths are appropriate for some indications.** It is important that you carefully read the instructions below for the indication you are treating to ensure you are using an appropriate dosage form and strength.

To enhance the tolerability of INTRON A, injections should be administered in the evening when possible.

To reduce the incidence of certain adverse reactions, acetaminophen may be administered at the time of injection.

Hairy Cell Leukemia (see DOSAGE AND ADMINISTRATION, General)

Dose: The recommended dose for the treatment of hairy cell leukemia is 2 million IU/m² administered intramuscularly or subcutaneously 3 times a week for up to 6 months. Patients with platelet counts of less than 50,000/mm³ should not be administered INTRON A intramuscularly, but instead by subcutaneous administration. Patients who are responding to therapy may benefit from continued

Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single use)	10 MIU/ml	IM, SC	N/A
Solution 10 MIU (single use)	10 MIU/ml	SC	N/A
Solution 18 MIU multidose	6MIU/ML	IM, SC	N/A
Solution 25 MIU multidose	10 MIU/ml	IM, SC	N/A
Pen 3 MIU/dose multidose	15 MIU/ml	SC	1.5, 3.0, 4.5
Pen 5 MIU/dose multidose	25 MIU/ml	SC	2.5, 5.0

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

Dose adjustment:

- If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy should be temporarily withheld until the adverse reactions abate and then resume at 50% (1 MIU/m² TIW).
- If severe adverse reactions persist or recur following dosage adjustment, INTRON A should be permanently discontinued.
- INTRON A should be discontinued for progressive disease or failure to respond after six month of treatment

Malignant Melanoma (see DOSAGE AND ADMINISTRATION, General)

INTRON A adjuvant treatment of malignant melanoma is given in two phases, induction and maintenance.

Induction Recommended Dose:

The recommended daily dose of INTRON A in induction is 20 million IU/m² as an intravenous infusion, over 20 minutes, 5 consecutive days per week, for 4 weeks (see Dose Adjustments below).

Dosage Forms for this Indication

Dosage Form	Concentration	Route
Powder 10 MIU	10 MIU/ml	IV
Powder 18 MIU	18 MIU/ml	IV
Powder 50 MIU	50 MIU/ml	IV

NOTE: INTRON A Solution for Injection in Vials or Multidose Pens is NOT recommended for intravenous administration and should not be used for the induction phase of malignant melanoma.

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

Dose adjustment:

NOTE: Regular laboratory testing should be performed to monitor laboratory abnormalities for the purpose of dose modifications (see **PRECAUTIONS-Laboratory Tests**).

- INTRON A should be withheld for severe adverse reactions, including granulocyte counts $>250\text{mm}^3$ but $<500\text{mm}^3$ or SGPT/SGOT $>5\text{-}10\text{x}$ upper limit of normal, until adverse reactions abate. INTRON A treatment should be restarted at 50% of the previous dose.
- INTRON A should be permanently discontinued for:
 - Toxicity that does not abate after withholding INTRON A
 - Severe adverse reactions which recur in patients receiving reduced doses of INTRON A
 - Granulocyte count $<250\text{mm}^3$ or SGPT/SGOT of $>10\text{x}$ upper limit of normal

Maintenance Recommended Dose:

The recommended dose of INTRON A for maintenance is 10 million IU/m² as a subcutaneous injection three times per week for 48 weeks (see Dose adjustment below).

Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single dose)*	10 MIU/ml	SC	
Powder 18 MIU (single dose)**	18 MIU/ml	SC	
Solution 10 MIU	10 MIU/ml	SC	
Solution 18 MIU multidose	6 MIU/ml	SC	
Solution 25 MIU multidose	10 MIU/ml	SC	
Pen 3 MIU/dose Multidose*	15 MIU/ml	SC	1.5, 3.0, 4.5, 6.0
Pen 5 MIU/dose Multidose	25 MIU/ml	SC	7.5, 10.0
Pen 10 MIU/dose Multidose	50 MIU/ml	SC	10.0, 15.0, 20.0

*Patients receiving 50% dose reduction only

**Patients receiving full dose only

NOTE: INTRON A powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

Dose adjustment:

NOTE: Regular laboratory testing should be performed to monitor laboratory abnormalities for the purpose of dose modifications (see **PRECAUTIONS-Laboratory Tests**).

- INTRON A should be withheld for severe adverse reactions, including granulocyte counts $>250\text{mm}^3$ but $<500\text{mm}^3$ or SGPT/SGOT $>5\text{-}10\text{x}$ upper limit of normal, until adverse reactions abate. INTRON A treatment should be restarted at 50% of the previous dose.
- INTRON A should be permanently discontinued for:
 - Toxicity that does not abate after withholding INTRON A
 - Severe adverse reactions which recur in patients receiving reduced doses of INTRON A
 - Granulocyte count $<250\text{mm}^3$ or SGPT/SGOT of $>10\text{x}$ upper limit of normal

Follicular Lymphoma (see DOSAGE and ADMINISTRATION, General)

Dose: The recommended dose of INTRON A for the treatment of follicular lymphoma is 5 million IU subcutaneously three times per week for up to 18 months in conjunction with anthracycline-containing chemotherapy regimen and following completion of the chemotherapy regimen.

Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single dose)	10 MIU/ml	SC	
Solution 10 MIU (single dose)	10 MIU/ml	SC	
Solution 18 MIU multidose	6 MIU/ml	SC	
Solution 25 MIU multidose	10 MIU/ml	SC	
Pen 5 MIU/dose multidose	25 MIU/ml	SC	2.5, 5.0
Pen 10 MIU/dose multidose	50 MIU/ml	SC	5.0

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

Dose adjustment:

- Doses of myelosuppressive drugs were reduced by 25% from a full-dose CHOP regimen, and cycle length increased by 33% (eg. From 21 to 28 days when alfa interferon was added to the regimen).
- Delay chemotherapy cycle if neutrophil count was $<1500/\text{mm}^3$ or platelet count was $<75,000/\text{mm}^3$

- INTRON A should be permanently discontinued if SGOT exceeds >5x the upper limit of normal or serum creatinine >2.0 mg/dl (see **WARNINGS**).
- Administration of INTRON A therapy should be withheld for a neutrophil count <1000/mm³, or a platelet count <50,000/mm³.
- INTRON A dose should be reduced by 50% (2.5 MIU TIW) for a neutrophil count >1000/mm³, but <1500/mm³. The INTRON A dose may be re-escalated to the starting dose (5 million IU TIW) after resolution of hematologic toxicity (ANC >1500/mm³).

Condylomata Acuminata (see **DOSAGE** and **ADMINISTRATION, General**)

Dose: The recommended dose is 1.0 million IU per lesion in a maximum of 5 lesions in a single course. The lesions should be injected three times weekly on alternate days for 3 weeks. An additional course may be administered at 12-16 weeks.

Dosage Forms for this Indication

Dosage Form	Concentration	Route
Powder 10MIU (single dose)	10 MIU/ml	IL
Solution 10 MIU (single dose)	10 MIU/ml	IL
Solution 25 MIU multidose	10 MIU/ml	IL

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

NOTE: Do not use the following formulations for this indication:

- the 18 million or 50 million IU Powder for Injection
- the 18 million IU multidose INTRON A Solution for Injection
- the Multidose Pens

Dose adjustment: None

Technique for Injection:

The injection should be administered intralesionally using a Tuberculin or similar syringe and a 25-to-30 gauge needle. The needle should be directed at the center of the base of the wart and at an angle almost parallel to the plane of the skin (approximately that in the commonly used PPD test). This will deliver the interferon to the dermal core of the lesion, infiltrating the lesion and causing a small wheal. Care should be taken not to go beneath the lesion too deeply; subcutaneous injection should be avoided, since this area is below the base of the lesion. Do not inject too superficially since this will result in possible leakage, infiltrating only the keratinized layer and not the dermal core.

AIDS-Related Kaposi's Sarcoma (see **DOSAGE and **ADMINISTRATION, General**)**

Dose: The recommended dose of INTRON A for Kaposi's Sarcoma is 30 million IU/m²/dose administered subcutaneously or intramuscularly three times a week until

disease progression or maximal response has been achieved after 16 weeks of treatment. Dose reduction is frequently required (see Dose adjustment below)

Dosage Form for this Indication

Dosage Form	Concentration	Route
Powder 50 MIU	50 MIU/ml	IM, SC

NOTE: INTRON A Solutions for Injection either in vials or in multidose pens should NOT be used for AIDS-Related Kaposi's Sarcoma.

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

Dose adjustment:

- INTRON A dose should be reduced by 50% or withheld for severe adverse reactions
- INTRON A may be resumed reduced dose if severe adverse reactions abate with interruption of dosing.
- INTRON A should be permanently discontinued if severe adverse reactions persist or if they recur in patients receiving a reduced dose.

Chronic Hepatitis C (see DOSAGE and ADMINISTRATION, General)

Dose: The recommended dose of INTRON A for the treatment of chronic hepatitis C is 3 million IU three times a week (TIW) administered subcutaneously or intramuscularly. In patients tolerating therapy with normalization of ALT at 16 weeks of treatment, INTRON A therapy should be extended to 18 to 24 months (72 to 96 weeks) at 3 million IU TIW to improve the sustained response rate (see **CLINICAL PHARMACOLOGY – Chronic Hepatitis C**). Patients who do not normalize their ALTs or have persistently high levels of HCV RNA after 16 weeks of therapy rarely achieve a sustained response with extension of treatment. Consideration should be given to discontinuing these patients from therapy.

See REBETRON Combination Therapy and REBETOL package inserts for dosing when used in combination with REBETOL (ribavirin, USP) for adults and pediatric patients.

Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Vial 18 MIU multidose	6 MIU/ml	IM, SC	N/A
Pen 3 MIU/dose multidose	15 MIU/ml	SC	1.5, 3.0

Dose adjustment: If severe adverse reactions develop during INTRON A treatment, the dose should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. If intolerance persists after dose adjustment, INTRON A therapy should be discontinued.

Chronic Hepatitis B Adults (see DOSAGE and ADMINISTRATION, General)

Dose: The recommended dose of INTRON A for the treatment of chronic hepatitis B is 30 to 35 million IU per week, administered subcutaneously or intramuscularly, either as 5 million IU daily (QD) or as 10 million IU three times a week (TIW) for 16 weeks.

Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single dose)	10 MIU/ml	IM, SC	
Solution 10 MIU (single dose)	10 MIU/ml	SC	
Solution 25 MIU multidose	10 MIU/ml	IM, SC	
Pen 5 MIU/dose multidose	25 MIU/ml	SC	2.5, 5.0, 10.0
Pen 10 MIU/dose multidose	50 MIU/ml	SC	5.0, 10.0

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

Chronic Hepatitis B Pediatrics (see DOSAGE and ADMINISTRATION, General)

Dose: The recommended dose of INTRON A for the treatment of chronic hepatitis B is 3 million IU/m² three times a week (TIW) for the first week of therapy followed by dose escalation to 6 million IU/m² TIW (maximum of 10 million IU TIW administered subcutaneously for a total duration of 16 to 24 weeks).

Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single dose)	10 MIU/ml	SC	
Solution 10 MIU (single dose)	10 MIU/ml	SC	
Solution 25 MIU multidose	10 MIU/ml	SC	
Pen 3 MIU/dose multidose	15 MIU/ml	SC	1.5, 3.0, 4.5, 6.0
Pen 5 MIU/dose multidose	25 MIU/ml	SC	2.5, 5.0, 7.5, 10.0
Pen 10 MIU/dose multidose	50 MIU/ml	SC	5.0, 10.0, 15.0, 20.0

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

Dose adjustment: If severe adverse reactions or laboratory abnormalities develop during INTRON A therapy, the dose should be modified (50% reduction) or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, INTRON A therapy should be discontinued.

For patients with decreases in white blood cell, granulocyte or platelet counts, the following guidelines for dose modification should be followed:

<u>INTRON A</u> <u>Dose</u>	<u>White Blood</u> <u>Cell Count</u>	<u>Granulocyte</u> <u>Count</u>	<u>Platelet</u> <u>Count</u>
Reduce 50%	$<1.5 \times 10^9 /L$	$<0.75 \times 10^9 /L$	$<50 \times 10^9 /L$
Permanently Discontinue	$<1.0 \times 10^9 /L$	$<0.5 \times 10^9 /L$	$<25 \times 10^9 /L$

INTRON A therapy was resumed at up to 100% of the initial dose when white blood cell, granulocyte, and/or platelet counts returned to normal or baseline values.

PREPARATION AND ADMINISTRATION

Reconstitution of INTRON A Powder for Injection

The reconstituted solution is clear and colorless to light yellow. The INTRON A powder reconstituted with Sterile Water for Injection, USP is a single-use vial and does not contain a preservative. **DO NO RE-ENTER VIAL AFTER WITHDRAWING THE DOSE. DISCARD UNUSED PORTION** (see **DOSAGE and ADMINISTRATION**). Once the dose from the single-dose vial has been withdrawn, the sterility of any remaining product can no longer be guaranteed. Pooling of unused portions of some medications has been linked to bacterial contamination and morbidity.

- **Intramuscular, Subcutaneous, or Intralesional Administration**

Inject 1ml Diluent (Sterile Water for Injection, USP) for INTRON A into the INTRON A vial. Swirl gently to hasten complete dissolution of the powder. The appropriate INTRON A dose should then be withdrawn and injected intramuscularly, subcutaneously, or intralesionally (see **MEDICATION GUIDE** for detailed instructions).

Please refer to the **Medication Guide** for detailed, step-by-step instructions on how to inject the INTRON A dose. After preparation and administration of the INTRON A injection, it is essential to follow the procedure for proper disposal of syringes and needles (see **MEDICATION GUIDE** for detailed instructions).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

- **Intravenous Infusion**

The infusion solution should be prepared immediately prior to use. Based on the desired dose, the appropriate vial strength(s) of INTRON A should be reconstituted with the diluent provided. Inject 1ml Diluent (Sterile Water for Injection, USP) for INTRON A, into the INTRON A vial. Swirl gently to hasten complete dissolution of the powder. The appropriate INTRON A dose should then be withdrawn and injected into a 100-ml bag of 0.9% Sodium Chloride Injection, USP. The final concentration of INTRON A should not be less than 10 million IU/100ml.

Please refer to the **Medication Guide** for detailed, step-by-step instructions on how to inject the INTRON A dose. After preparation and administration of INTRON A, it is essential to follow the procedure for proper disposal of syringes and needles.

INTRON A Solution for Injection in Vials

INTRON A Solution for Injection is supplied in a single-use vial and two multidose vials. The solutions for injection do not require reconstitution prior to administration; the solution is clear and colorless.

The appropriate dose should be withdrawn from the vial and injected intramuscularly, subcutaneously, or intralesionally.

The single-use 10 million IU vial is supplied with B-D Safety-Lok* syringes. The Safety-Lok* syringe contains a plastic safety sleeve to be pulled over the needle after use. The syringe locks with an audible click when the green stripe on the safety sleeve covers the red stripe on the needle. The B-D Safety-Lok* syringes provided with the 10 MIU Solution for Injection cannot be used for IM injections.

INTRON A Solution for Injection is not recommended for intravenous administration.

Solution for Injection in Multidose Pens

The INTRON A Solution for Injection multidose pens are designed to deliver 3-12 doses depending on the individual dose using a simple dial mechanism and are for subcutaneous injections only. Only the needles provided in the packaging should be used for the INTRON A Solution for Injection multidose pen. A new needle is to be used each time a dose is delivered using the pen. To avoid the possible transmission of disease, each INTRON A Solution for Injection multidose pen is for single patient use only.

Please refer to the **Medication Guide** for detailed, step-by-step instructions on how to inject the INTRON A dose. After preparation and administration of INTRON A, it is essential to follow the procedure for proper disposal of syringes and needles.

HOW SUPPLIED

INTRON A Powder for Injection

INTRON A Interferon alfa-2b, recombinant Powder for Injection, 10 million IU per vial and Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (Sterile Water for Injection, USP) 1 mL per vial; boxes containing 1 INTRON A vial and 1 vial of INTRON A Diluent (NDC 0085-0571-02).

INTRON A Interferon alfa-2b, recombinant Powder for Injection, 18 million IU per vial and Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (Sterile Water for Injection, USP) 1 mL per vial; boxes containing 1 vial of INTRON A and one vial of INTRON A Diluent (NDC 0085-1110-01).

INTRON A Interferon alfa-2b, recombinant Powder for Injection, 50 million IU per vial and Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (Sterile Water for Injection, USP) 1 mL per vial; boxes containing 1 INTRON A vial and 1 vial of INTRON A Diluent (NDC 0085-0539-01).

INTRON A Solution for Injection in Multidose Pens

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 6 doses of 3 million IU (18 million IU) multidose pen (22.5 million IU per 1.5 mL per pen); boxes containing 1 INTRON A multidose pen, six disposable needles and alcohol swabs (NDC 0085-1242-01).

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 6 doses of 5 million IU (30 million IU) multidose pen (37.5 million IU per 1.5 mL per pen) boxes containing 1 INTRON A multidose pen, six disposable needles and alcohol swabs (NDC 0085-1235-01).

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 6 doses of 10 million IU (60 million IU) multidose pen (75 million IU per 1.5 mL per pen); boxes containing 1 INTRON A multidose pen, six disposable needles and alcohol swabs (NDC 0085-1254-01).

INTRON A Solution for Injection in Vials

INTRON A Interferon alfa-2b, recombinant Solution for Injection INTRON A, Pak-10, containing 6 INTRON A vials, 10 million IU per vial, and 6 B-D Safety-Lok syringes with a safety sleeve (NDC 0085-1179-02).

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 18 million IU multidose vial (22.8 million IU per 3.8 mL per vial); boxes containing 1 vial of INTRON A Solution for Injection (NDC 0085-1168-01).

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 25 million IU multidose vial (32 million IU per 3.2 mL per vial); boxes containing 1 vial of INTRON A Solution for Injection (NDC 0085-1133-01).

Storage

- **INTRON A Powder for Injection/Reconstitution**
Intron A Powder for Injection should be stored at 2° to 8°C (36° to 46°F). After reconstitution, the solution should be used immediately, but may be stored up to 24 hours at 2° to 8°C (36° to 46°F).
- **INTRON A Solution for Injection in Vials**
Intron A Solution for Injection in Vials should be stored at 2° to 8°C (36° to 46°F).
- **INTRON A Solution for Injection in Multidose Pens**
Intron A Solution for Injection in Multidose Pens should be stored at 2° to 8°C (36° to 46°F).

Schering Corporation
Kenilworth, NJ 07033 USA

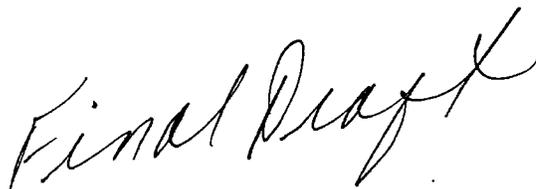
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2

3 **MEDICATION GUIDE**
4

5 **INTRON® A**

6 (Interferon alfa-2b, recombinant)
7

8 **Including appendix with instructions for using INTRON A Powder for Injection**
9

10 Read this Medication Guide carefully before you start to take INTRON A (In-tron
11 aye) for Injection alone or INTRON A in combination with REBETOL (REB-eh-tole)
12 (ribavirin, USP) Capsules. Read the Medication Guide each time you refill your
13 prescription because there may be new information. The information in this
14 Medication Guide does not take the place of talking with your healthcare provider.
15
16

17 If you are taking INTRON A and REBETOL combination therapy, also read the
18 medication guide for REBETOL (ribavirin, USP) Capsules.
19

20 **What is the most important information I should know about INTRON A?**
21

22 INTRON A is a treatment for some people who have hairy cell leukemia, malignant
23 melanoma, follicular lymphoma, AIDS-related Kaposi's sarcoma, chronic hepatitis B,
24 chronic hepatitis C and condylomata acuminata. If you have chronic hepatitis C,
25 your healthcare provider may prescribe INTRON A in combination with REBETOL.
26 INTRON A used by itself or with REBETOL can help you, but can also have serious
27 side effects and may cause death in rare cases. Before starting treatment, you
28 should talk to your healthcare provider about the possible benefits and possible side
29 effects of INTRON A alone or in combination with REBETOL, to decide if this
30 treatment is right for you. While taking INTRON A alone or in combination with
31 REBETOL, you need to see a healthcare provider regularly for medical examinations
32 and lab tests to make sure the treatment is working and to check for side effects.
33

34 **You should call your doctor immediately if you develop any of these
35 conditions while taking INTRON A:**

- 36 • You become pregnant or if you are a male and your female partner becomes
37 pregnant
38 • New or worsening mental health problems such as thoughts about hurting or
39 killing yourself or others
40 • Decreased vision
41 • Trouble breathing or chest pain
42 • Severe stomach or lower back pain
43 • Bloody diarrhea or bloody bowel movements
44 • High fever
45 • Easy bruising or bleeding
46

47 The most serious possible side effects of INTRON A include:
48

49 **RISK TO PREGNANCY.** Combination INTRON A and REBETOL therapy can
50 cause death, serious birth defects or other harm to your unborn child. If you
51 are pregnant, you or your male partner must not take INTRON A and REBETOL
52 combination therapy. You must not become pregnant while either you or your
53 partner are taking the combination of INTRON A and REBETOL and for 6
54 months after you stop taking the combination. If you are a woman of
55 childbearing age you must have negative pregnancy tests immediately before
56 starting treatment, during treatment and for 6 months after you have stopped
57 treatment. You should use two forms of birth control during and for 6 months
58 after you have stopped treatment. If you are a man taking INTRON
59 A/REBETOL combination therapy, one of the two forms of birth controls
60 should be a condom. You must use birth control even if you believe that you
61 are not fertile or that your fertility is low. You should talk to your doctor about
62 birth control for you and your partner. If you or your partner becomes
63 pregnant while either of you is being treated or within 6 months of stopping
64 treatment tell your doctor right away.

65
66 **Mental health problems and suicide.** INTRON A may cause patients to develop
67 mood or behavioral problems. These can include irritability (getting easily upset)
68 and depression (feeling low, feeling bad about yourself, or feeling hopeless). Some
69 patients may have aggressive behavior. Former drug addicts may fall back into drug
70 addiction or overdose. Some patients think about hurting or killing themselves or
71 other people. Some patients have killed themselves (suicide) or hurt themselves or
72 others. You must tell your doctor if you are being treated for a mental illness or had
73 treatment in the past for any mental illness, including depression and suicidal
74 behavior. You should also tell your doctor if you have ever been addicted to drugs
75 or alcohol.

76
77 **Eye problems.** If you notice any changes in your eyesight such as difficulty seeing,
78 it could mean that your eyes are being affected, so you should call your doctor right
79 away.

80
81 **Heart problems.** Some patients taking INTRON A may develop problems with their
82 heart, including low blood pressure, fast heart rate, and very rarely, heart attacks.
83 Tell your doctor if you have had any heart problems in the past.

84
85 **Blood problems.** INTRON A commonly lowers two types of blood cells (white
86 blood cells and platelets). In some patients, these blood counts may fall to
87 dangerously low levels. If your blood cell counts become very low, you could get
88 infections or have bleeding problems.

89
90 If you are taking INTRON A and REBETOL combination therapy, REBETOL can
91 cause a drop in your number of red blood cells (anemia). A very low red blood cell
92 count can be dangerous especially if you have heart or breathing problems.
93 For other possible side effects of INTRON A. see "What are the possible side
94 effects of INTRON A?" in this Medication Guide.

95

96 What Is INTRON A?

97

98 The INTRON A product contains a man-made protein called interferon. Interferon is
99 a protein that is part of the body's immune system that "interferes" with the growth of
100 viruses or cancer cells.

101

102 It is not known if INTRON A or INTRON A/REBETOL combination therapy can cure
103 hepatitis B or C (permanently eliminate the virus) or if it can prevent liver failure or
104 liver cancer that is caused by hepatitis B or C infection.

105

106 It is also not known if INTRON A or INTRON A/REBETOL combination therapy will
107 prevent one infected person from infecting another person with hepatitis B or C.

108

109 Who should not take INTRON A?

110

111 Do not take the INTRON A alone or in combination with REBETOL if you:

112

- 113 • are pregnant, planning to get pregnant, or breast-feeding.
- 114 • are a male patient on combination therapy and have a female sexual partner who
115 is pregnant or plans to become pregnant while you are being treated with
116 REBETOL or during the 6 months after your treatment has ended.
- 117 • have autoimmune hepatitis (hepatitis caused by your immune system attacking
118 your liver) or unstable liver disease (yellowing of the skin and eyes, swelling of
119 the abdomen).
- 120 • had an allergic reaction to another alpha interferon or ribavirin or are allergic to
121 any of the ingredients in INTRON A or REBETOL.

122

123 **If you have any of the following conditions or serious medical problems, tell**
124 **your doctor before taking INTRON A alone or in combination with REBETOL:**

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- depression or anxiety
- eye problems
- sleep problems
- high blood pressure
- previous heart attack, or other heart problems
- liver problems (other than hepatitis B or C)
- any kind of autoimmune disease (where the body's immune system attacks the
body's own cells), such as psoriasis, sarcoidosis, systemic lupus erythematosus,
rheumatoid arthritis
- thyroid problems
- diabetes
- colitis (inflammation of the bowels)
- cancer
- hepatitis B or C infection
- HIV infection (the virus that causes AIDS)
- kidney problems
- bleeding problems
- alcoholism

- 143 • drug abuse or addiction
- 144 • body organ transplant and are taking medicine that keeps your body from
- 145 rejecting your transplant (suppresses your immune system).
- 146 • high blood triglycerides (fat particles normally found in you blood)

147

148 How should I take INTRON A?

149

150 To get the most benefit from this medicine, it is important that you take INTRON A
151 exactly as your doctor tells you. Your doctor will decide your dose of INTRON A and
152 how often you will take it. Do not take more than your prescribed dose. INTRON A is
153 given as an injection either under the skin (subcutaneous) or into a muscle
154 (intramuscular). You should be completely comfortable with how to prepare and
155 measure your dose of INTRON A and how to inject yourself before you use INTRON
156 A for the first time. Your healthcare provider will train you on how to use and inject
157 INTRON A properly.

158

159 INTRON A comes in different strengths and different forms (a powder in a vial, a
160 solution in a vial and a multidose pen). Your doctor will determine which form is best
161 for you. The instructions for giving a dose of INTRON A are at the end of this leaflet.

162

163 If you miss a dose of INTRON A, take the missed dose as soon as possible during
164 the same day or the next day, then continue on your regular dosing schedule. If
165 several days go by after you miss a dose, check with your doctor to see what to do.
166 **Do not double your next dose** or take more than your prescribed dose without
167 talking to your doctor. Call your doctor right away if you take more than your
168 prescribed dose. Your doctor may wish to examine you more closely and take blood
169 for testing.

170

171 If you are taking INTRON A in combination with REBETOL, you should also read the
172 Medication Guide for REBETOL (ribavirin, USP) for more information about side
173 effects and how to take REBETOL. **REBETOL capsules should be taken twice a**
174 **day with food.** Taking REBETOL with food helps your body take up more of the
175 medicine. Taking REBETOL at the same time of day every day will help keep the
176 amount of medicine in your body at a steady level. This can help your doctor decide
177 how your treatment is working and how to change the dose number of REBETOL
178 ~~capsules~~ you take if you have side effects. If you miss a dose of REBETOL, take the
179 missed dose as soon as possible during the same day. If an entire day has passed,
180 check with your doctor about what to do. **Do not double your next dose.**

181

182 You must see your doctor on a regular basis for blood tests so your doctor can
183 check how the treatment is working for you and to check for side effects.

183

184 Tell your doctor if you are taking or planning to take other prescription or non-
185 prescription medicines, including vitamin and mineral supplements and herbal
186 medicines.

187

188 What should I avoid while taking INTRON A?

189

- 190 • Avoid becoming pregnant while taking the INTRON A. INTRON A alone and
INTRON A taken in combination with REBETOL may harm your unborn child or

191 cause you to lose your baby (miscarry). If you or your partner becomes pregnant
192 during treatment or during the 6 months after treatment with INTRON
193 A/REBETOL combination therapy, immediately report the pregnancy to your
194 doctor. Your doctor will make decisions about your treatment.

- 195 • Do not breast-feed your baby while taking INTRON A.

196

197 What are the possible side effects of INTRON A?

198

199 Possible, serious side effects include:

200

- 201 • **Risk to pregnancy, mental health problems, including suicide, blood**
202 **problems, and heart problems and eye problems.** *see "What is the most*
203 *important information I should know about INTRON A?"*
- 204 • **Other body organ problems.** Certain symptoms like severe pain in the middle
205 of your body, nausea, and vomiting may mean that your liver or pancreas is
206 being damaged. A few patients have lung problems such as pneumonia
207 (inflammation of the lung tissue), and inflammation of the kidney. If you are short
208 of breath, coughing or have severe stomach or back pains or a fever, you should
209 call your doctor right away.
- 210 • **Thyroid problems.** Some patients develop changes in the function of their
211 thyroid. Symptoms of thyroid changes include the inability to concentrate, feeling
212 cold or hot all the time, a change in your weight and changes to your skin.
- 213 • **New or worsening autoimmune disease.** Some patients taking INTRON A
214 develop autoimmune diseases (a condition where the body's immune cells attack
215 other cells or organs in the body), including rheumatoid arthritis, systemic lupus
216 erythematosus, sarcoidosis, and psoriasis. In some patients who already have
217 an autoimmune disease, the disease may worsen while on INTRON A.

218

219 Common but less serious side effects include:

220

- 221 • **Flu-like symptoms.** Most patients who take INTRON A have "flu-like"
222 symptoms (headache, muscle aches, tiredness, and fever) that usually lessen
223 after the first few weeks of therapy. You can reduce some of these symptoms by
224 injecting your INTRON A dose at bedtime. Over-the-counter pain and fever
225 medications can be used to prevent or reduce the fever and headache. If your
226 fever does not go away you should tell your doctor.
- 227 • **Extreme fatigue (tiredness).** Many patients become extremely tired while on
228 INTRON A.
- 229 • **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.
- 230 • **Blood sugar problems.** Some patients develop problems with the way their
231 body controls their blood sugar and may develop high blood sugar or diabetes.
- 232 • **Skin reactions.** Redness, swelling, and itching are common at the site of
233 injection. If after several days these symptoms do not disappear, contact your
234 doctor. You may get a rash during therapy. If this occurs, your doctor may
235 recommend medicine to treat the rash.
- 236 • **Hair thinning.** Hair thinning is common during INTRON A treatment. Hair loss
237 stops and hair growth returns after therapy is stopped.

238

239 These are not all the side effects of INTRON A or INTRON A/REBETOL combination
240 therapy. Your healthcare provider can give you a more complete list.
241

242 **General advice about prescription medicines**

243 Medicines are sometimes prescribed for purposes other than those listed in a
244 Medication Guide. If you have any concerns about the INTRON A product, ask
245 healthcare provider. Your health care provider can give you additional information
246 about INTRON A. Do not use INTRON A for a condition for which it was not
247 prescribed. Do not share this medication with other people.
248

249 This Medication Guide has been approved by the U.S. Food and Drug
250 Administration.
251

252 Manufactured by: Schering Corporation Kenilworth, NJ 07033 USA
253

254 Issued: XX/XX
255

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262 **Medication Guide Appendix: Instructions for Preparing and Giving a Dose of**
263 **INTRON A Powder for Injection**
264

- 265 • INTRON A medication has been supplied to you as a powder form that requires
266 you to add the supplied liquid (DILUENT) to the powder. The liquid (DILUENT) is
267 supplied to you in a vial.
268

269 **The INTRON A Powder for Injection may be supplied to you in 10 million IU, 18**
270 **million IU, or 50 million IU vials.** These packages contain 1 vial of INTRON A
271 powder and 1 vial of DILUENT (Sterile Water for Injection, USP). Syringes are not
272 supplied to you. Talk to your healthcare provider about what syringes you should
273 use
274

275 **Storing INTRON A Powder for Injection**

276 Before and after reconstitution, INTRON A Powder for Injection should be stored in
277 the refrigerator between 2° and 8°C (36° and 46°F). **DO NOT FREEZE.**
278

279 **NOTE: INTRON A Powder for Injection does not contain a preservative. The**
280 **vial must be discarded after reconstitution and withdrawal of a single dose.**
281

282

283 **Preparing a Dose of INTRON A Powder for Injection**

284

285

1. Find a well lit, clean, flat working surface such as a table. Collect the supplies you will need for an injection:

286

287

288

- A vial of INTRON A powder
- A vial of DILUENT (Sterile Water for Injection, USP)
- A single-use, disposable syringe, as prescribed by your healthcare provider
- A cotton ball or gauze
- Two Alcohol swabs
- A puncture-proof disposable container

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2. Before removing the vials from the carton, check the expiration date printed on the carton to make sure that the expiration date has not passed. Do not use if the expiration date has passed.

296

297

298

3. Wash your hands with soap and warm water. It is important to keep your work area, your hands and injection site clean to minimize the risk of infection.

299

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4. Gently warm the DILUENT vial by slowly rolling the vial in the palm of your hands for one minute.

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5. Remove the protective caps from both vials (INTRON A powder and the supplied DILUENT). Clean the rubber stopper on the top of each vial with an alcohol swab.

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6. Open the syringe package and remove the syringe.

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7. Remove the needle cover from the syringe. Fill the syringe with air by pulling the plunger back to mark on the syringe that matches the dose prescribed by your healthcare provider.

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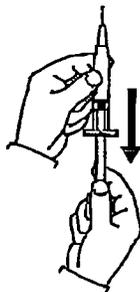
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8. Hold the DILUENT vial on your flat working surface without touching the cleaned rubber stopper with your hands.

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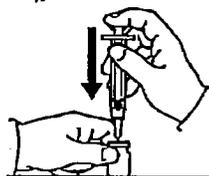
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9. Insert the needle straight down through the middle of the rubber stopper of the vial containing the DILUENT. Slowly inject all the air from the syringe into the air space above the DILUENT.

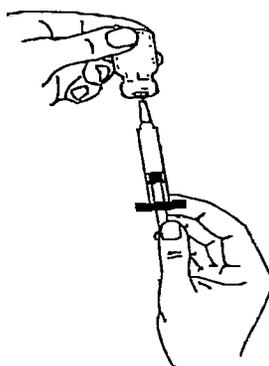
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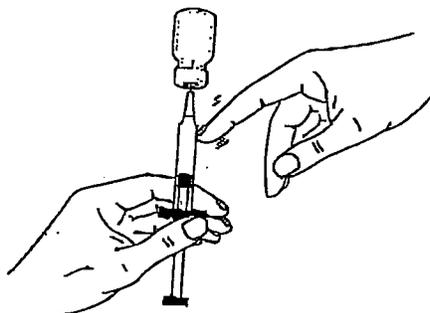
10. Keep the needle in the vial and turn the vial upside down. Make sure the tip of the needle is in the DILUENT. Slowly pull the plunger back to fill the syringe with DILUENT to the number (mL or cc) that your healthcare provider instructed you to use.



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11. With the needle still inserted in the vial, check the syringe for air bubbles. If there are any air bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to remove the air bubbles. If you push DILUENT back into the vial, slowly pull back on the plunger to again draw the correct amount of DILUENT back into the syringe.

Page 9



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12. Remove the needle from the vial. Do not let the syringe touch anything.

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13. Without touching the cleaned rubber stopper, insert the needle through the middle of the rubber stopper and gently place the needle tip, at an angle, against the side of the INTRON A powder vial.

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14. Slowly push the plunger down to inject the DILUENT. The stream of liquid should run down the slides of the glass vial. **DO NOT INJECT THE DILUENT DIRECTLY AT THE WHITE POWDER.**

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15. Do not remove the needle from the vial.

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16. To dissolve the white powder, gently swirl the INTRON A vial in a circular motion until the powder is completely dissolved. **DO NOT SHAKE.** If the solution is foamy, wait a few minutes until the bubbles have settled before withdrawing your dose from the vial.

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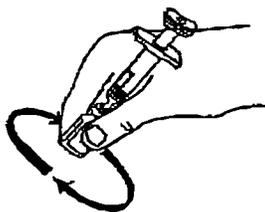
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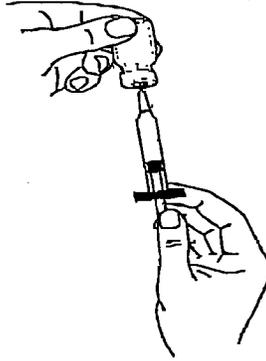
17. Check the solution inside the vial of the INTRON A. The solution should be clear and colorless to light yellow, without particles. Do not use the INTRON A if the

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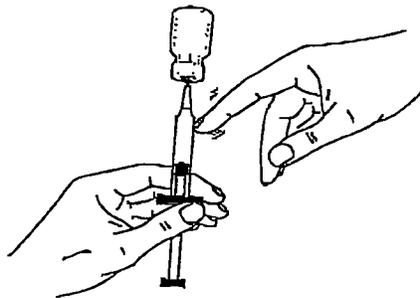
393 medicine is cloudy, has particles or is any color besides clear and colorless to
394 light yellow.

395 18. With the needle in the vial, turn the vial upside down. Make sure the tip of the
396 needle is in the INTRON A solution. Slowly pull the plunger back to fill the syringe
397 with the INTRON A solution to the number (mL or cc) that your healthcare
398 provider has prescribed.
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404 19. With the needle still inserted in the vial, check the syringe for air bubbles. If there
405 are any air bubbles, gently tap the syringe with your finger until the air bubbles
406 rise to the top of the syringe.
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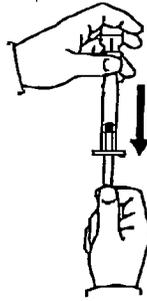


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411 20. Slowly push the plunger up to remove the air bubbles. If you push solution back
412 into the vial, slowly pull back on the plunger again to draw the correct amount of
413 INTRON A solution back into the syringe.

414 21. Do not remove the needle from the vial. Lay the vial and syringe on its side on
415 your flat work surface until you are ready to inject the INTRON A solution.

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428 **Choosing an Injection site**

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Based on your treatment, your health care provider will tell you if you should inject a dose of INTRON A subcutaneously (under the skin) or intramuscularly (into the muscle). If it is too difficult for you to inject, ask someone who has been trained to give injections to help you.

436 **FOR SUBCUTANEOUS INJECTION**

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The best sites for injection are areas on your body with a layer of fat between skin and muscle such as:

- the front of your middle thighs
- the outer area of your upper arms
- the abdomen, except around the navel



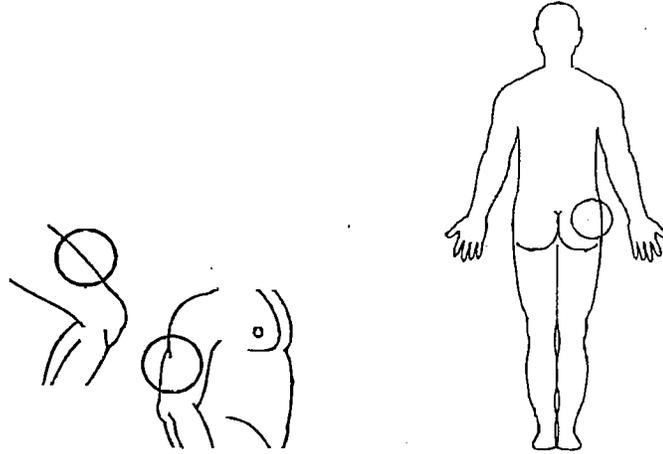
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446 **FOR INTRAMUSCULAR INJECTION**

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The best sites for injection into your muscle are:

- the front of the middle thighs
- the upper arms
- the upper outer areas of the buttocks



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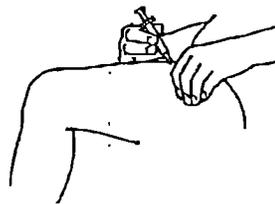
You should use a different site each time you inject INTRON A to avoid soreness at any one site. Do not inject INTRON A into an area where the skin is irritated, red, bruised, infected or has scars, stretch marks or lumps.

Injection the Dose of INTRON A

1. Clean the injection site with a new alcohol swab.
2. Pick up the vial and syringe from your flat work surface. Remove the syringe and needle from the vial. Hold the syringe in the hand that you will use to inject INTRON A. Do not touch the needle or allow it to touch the work surface. If you are using a Safety-Lok* syringe, make sure the safety sleeve is pushed against the syringe flange so that the needle is fully exposed.
3. With your free hand, pinch a fold of the skin at the cleaned injection site.

FOR SUBCUTANEOUS INJECTION:

- 4a. Hold the syringe (like a pencil) at a **45-degree angle** to the skin. With a quick "dart-like" motion push the needle into the skin.



FOR INTRAMUSCULAR INJECTION:

- 4b. Hold the syringe (like a pencil) at a **90-degree angle** to the skin. With a quick "dart-like" motion, push the needle into the muscle.

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5. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull the plunger back slightly. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject INTRON A. Withdraw the needle and discard the syringe in the puncture-proof container. *See "How should I dispose of materials used to inject INTRON A?"* Prepare a new dose of INTRON A using a new INTRON A Powder for Injection vial and prepare a new injection site.

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6. If no blood is present in the syringe, inject the medicine by gently pushing the plunger all the way down until the syringe is empty.

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7. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds. Do not massage the injection site. If there is bleeding, cover the injection site with a bandage.

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8. Dispose of syringe and needle. *See "How should I dispose of materials used to inject INTRON A?"*

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9. It is important to check your injection site approximately two hours after your injection for redness, swelling, or tenderness. These are signs of inflammation that you may need to talk to your healthcare provider about if they do not go away.

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How should I dispose of materials used to inject INTRON A?

There may be special state and local laws for disposal of used needles and syringes. Your healthcare provider should provide you with instructions on how to properly dispose of your used syringes and needles. Always follow these instructions. The instructions below should be used as a general guide for proper disposal.

- The needles and syringes should never be reused.
- Place all used needles and syringes in a puncture-proof disposable container that is available through your pharmacy or healthcare provider. You may also

528 use a hard plastic container with a screw-on cap (like a laundry detergent
529 container).
530 • DO NOT use glass or clear plastic containers for disposal of needles and
531 syringes.
532

533 The container should be clearly labeled as "USED SYRINGES AND NEEDLES."
534 When the container is about two-thirds full, tighten the lid. Tape the cap or lid to
535 make sure it does not come off. Dispose of the container as instructed by your
536 healthcare provider. DO NOT throw the container in your household trash. DO NOT
537 recycle.

538 • **Always keep the container out of reach of children**



1 F-XXXXXXXX

2
3 **MEDICATION GUIDE**

4
5 **INTRON® A**
6 (Interferon alfa-2b, recombinant)
7

8 **Including appendix with instructions for using INTRON A Multidose Pen for**
9 **Injection**

10
11 Read this Medication Guide carefully before you start to take INTRON A (In-tron
12 aye) for Injection alone or INTRON A in combination with REBETOL (REB-eh-tole)
13 (ribavirin, USP) Capsules. Read the Medication Guide each time you refill your
14 prescription because there may be new information. The information in this
15 Medication Guide does not take the place of talking with your healthcare provider.
16

17 If you are taking INTRON A and REBETOL combination therapy, also read the
18 Medication Guide for REBETOL (ribavirin, USP) Capsules.
19
20

21 **What is the most important information I should know about INTRON A?**
22

23 INTRON A is a treatment for some people who have hairy cell leukemia, malignant
24 melanoma, follicular lymphoma, AIDS-related Kaposi's sarcoma, chronic hepatitis B,
25 chronic hepatitis C and condylomata acuminata. If you have chronic hepatitis C, your
26 healthcare provider may prescribe INTRON A in combination with REBETOL.
27 INTRON A used by itself or with REBETOL can help you but can also have serious
28 side effects and may cause death in rare cases. Before starting treatment, you
29 should talk to your healthcare provider about the possible benefits and possible side
30 effects of INTRON A alone or in combination with REBETOL, to decide if this
31 treatment is right for you. While taking INTRON A alone or in combination with
32 REBETOL, you need to see a healthcare provider regularly for medical examinations
33 and lab tests to make sure the treatment is working and to check for side effects.
34

35 **You should call your doctor immediately if you develop any of these**
36 **conditions while taking INTRON A:**

- 37
- 38 • You become pregnant or if you are a male and your female partner becomes pregnant
 - 39 • New or worsening mental health problems such as thoughts about hurting or
 - 40 killing yourself or others
 - 41 • Decreased vision
 - 42 • Trouble breathing or chest pain
 - 43 • Severe stomach or lower back pain
 - 44 • Bloody diarrhea or bloody bowel movements
 - 45 • High fever
 - 46 • Easy bruising or bleeding
- 47

48 The most serious possible side effects of INTRON A include:

49

50 **RISK TO PREGNANCY.** Combination INTRON A and REBETOL therapy can
51 cause death, serious birth defects or other harm to your unborn child. If you
52 are pregnant, you or your male partner must not take INTRON A and REBETOL
53 combination therapy. You must not become pregnant while either you or your
54 partner are taking the combination of INTRON A and REBETOL and for 6
55 months after you stop taking the combination. If you are a woman of
56 childbearing age you must have negative pregnancy tests immediately before
57 starting treatment, during treatment and for 6 months after you have stopped
58 treatment. You should use two forms of birth control during and for 6 months
59 after you have stopped treatment. If you are a man taking INTRON
60 A/REBETOL combination therapy, one of the two forms of birth controls
61 should be a condom. You must use birth control even if you believe that you
62 are not fertile or that your fertility is low. You should talk to your doctor about
63 birth control for you and your partner. If you or your partner become pregnant
64 while either of you is being treated or within 6 months of stopping treatment
65 tell your doctor right away.

66

67 **Mental health problems and suicide.** INTRON A may cause patients to develop
68 mood or behavioral problems. These can include irritability (getting easily upset)
69 and depression (feeling low, feeling bad about yourself, or feeling hopeless). Some
70 patients may have aggressive behavior. Former drug addicts may fall back into drug
71 addiction or overdose. Some patients think about hurting or killing themselves or
72 other people. Some patients have killed (suicide) or hurt themselves or others. You
73 must tell your doctor if you are being treated for a mental illness or had treatment in
74 the past for any mental illness, including depression and suicidal behavior. You
75 should also tell your doctor if you have ever been addicted to drugs or alcohol.

76

77 **Eye problems.** If you notice any changes in your eyesight such as difficulty seeing,
78 it could mean that your eyes are being affected so you should call your doctor right
79 away.

80

81 **Heart problems.** Some patients taking INTRON A may develop problems with their
82 heart, including low blood pressure, fast heart rate, and very rarely, heart attacks.
83 Tell your doctor if you have had any heart problems in the past.

84

85 **Blood problems.** INTRON A commonly lowers two types of blood cells (white
86 blood cells and platelets). In some patients, these blood counts may fall to
87 dangerously low levels. If your blood cell counts become very low, you could get
88 infections or have bleeding problems.

89

90 If you are taking INTRON A and REBETOL combination therapy, REBETOL can
91 cause a drop in your number of red blood cells (anemia). A very low red blood cell
92 count can be dangerous especially if you have heart or breathing problems.

93

94 *For other possible side effects of INTRON A see "What are the possible side effects*
95 *of INTRON A" in this Medication Guide.*

96

97 What Is INTRON A?

98

99 The INTRON A product contains a man-made protein called interferon. Interferon is
100 a protein that is part of the body's immune system that "interferes" with the growth of
101 viruses or cancer cells.

102

103 It is not known if INTRON A or INTRON A/REBETOL combination therapy can cure
104 hepatitis B or C (permanently eliminate the virus) or if it can prevent liver failure or
105 liver cancer that is caused by hepatitis B or C infection.

106 It is also not known if INTRON A or INTRON A/REBETOL combination therapy will
107 prevent one infected person from infecting another person with hepatitis B or C.

108

109 Who should not take INTRON A?

110 Do not take the INTRON A alone or in combination with REBETOL if you:

111

- 112 • are pregnant, planning to get pregnant, or breast-feeding.
- 113 • are a male patient on combination therapy and have a female sexual partner who
114 is pregnant or plans to become pregnant while you are being treated with
115 REBETOL or during the 6 months after your treatment has ended.
- 116 • have autoimmune hepatitis (hepatitis caused by your immune system attacking
117 your liver) or unstable liver disease (yellowing of the skin and eyes, swelling of
118 the abdomen).
- 119 • had an allergic reaction to another alpha interferon or ribavirin or are allergic to
120 any of the ingredients in INTRON A or REBETOL.

121

122 **If you have any of the following conditions or serious medical problems, tell**
123 **your doctor before taking INTRON A alone or in combination with REBETOL:**

- 124 • depression or anxiety
- 125 • eye problems
- 126 • sleep problems
- 127 • high blood pressure
- 128 • previous heart attack, or other heart problems
- 129 • liver problems (other than hepatitis B or C infection)
- 130 • any kind of autoimmune disease (where the body's immune system attacks the
131 body's own cells), such as psoriasis, sarcoidosis, systemic lupus erythematosus,
132 rheumatoid arthritis
- 133 • thyroid problems
- 134 • diabetes
- 135 • colitis (inflammation of the bowels)
- 136 • cancer
- 137 • hepatitis B or C infection
- 138 • HIV infection (the virus that causes AIDS)
- 139 • kidney problems
- 140 • bleeding problems
- 141 • alcoholism
- 142 • drug abuse or addiction

- 143 • body organ transplant and are taking medicine that keeps your body from
144 rejecting your transplant (suppresses your immune system).
145 • high blood triglycerides (fat particles normally found in your blood)
146

147 How should I take INTRON A?

148

149 To get the most benefit from this medicine, it is important that you take INTRON A
150 exactly as your doctor tells you. Your doctor will decide your dose of INTRON A and
151 how often you will take it. Do not take more than your prescribed dose. INTRON A is
152 given as an injection either under the skin (subcutaneous) or into a muscle
153 (intramuscular). You should be completely comfortable with how to prepare and
154 measure your dose of INTRON A and how to inject yourself before you use INTRON
155 A for the first time. Your healthcare provider will train you on how to use and inject
156 INTRON A properly.
157

158 INTRON A comes in different strengths and different forms (a powder in a vial, a
159 solution in a vial and a multidose pen). Your doctor will determine which form is best
160 for you. The instructions for giving a dose of INTRON A are at the end of this leaflet.
161

162 If you miss a dose of INTRON A, take the missed dose as soon as possible during
163 the same day or the next day, then continue on your regular dosing schedule. If
164 several days go by after you miss a dose, check with your doctor to see what to do.
165 **Do not double your next dose** or take more than your prescribed dose without
166 talking to your doctor. Call your doctor right away if you take more than your
167 prescribed dose. Your doctor may wish to examine you more closely and take blood
168 for testing.
169

170 If you are taking INTRON A in combination with REBETOL, you should also read the
171 Medication Guide for REBETOL (ribavirin, USP) for more information about side
172 effects and how to take REBETOL. **REBETOL capsules should be taken twice a**
173 **day with food.** Taking REBETOL with food helps your body take up more of the
174 medicine. Taking REBETOL at the same time of day every day will help keep the
175 amount of medicine in your body at a steady level. This can help your doctor decide
176 how your treatment is working and how to change the dose number of REBETOL
177 ~~capsules~~ you take if you have side effects. If you miss a dose of REBETOL, take the
178 missed dose as soon as possible during the same day. If an entire day has passed,
179 check with your doctor about what to do. **Do not double your next dose.**

180 You must see your doctor on a regular basis for blood tests so your doctor can
181 check how the treatment is working for you and to check for side effects.
182

183 Tell your doctor if you are taking or planning to take other prescription or non-
184 prescription medicines, including vitamin and mineral supplements and herbal
185 medicines.
186

187 What should I avoid while taking INTRON A?

- 188 • Avoid becoming pregnant while taking the INTRON A. INTRON A alone and
189 INTRON A taken in combination with REBETOL may harm your unborn child or
190 cause you to lose your baby (miscarry). If you or your partner becomes pregnant

191 during treatment or during the 6 months after treatment with INTRON
192 A/REBETOL combination therapy, immediately report the pregnancy to your
193 doctor. Your doctor will make decisions about your treatment.

- 194 • Do not breastfeed your baby while taking INTRON A.

195

196 What are the possible side effects of INTRON A?

197

198 Possible, serious side effects include:

199

- 200 • **Risk to pregnancy, mental health problems, including suicide, blood**
201 **problems, and heart problems and eye problems.** see "What is the most
202 *important information I should know about INTRON A?*"
- 203 • **Other body organ problems.** Certain symptoms like severe pain in the middle
204 of your body, nausea, and vomiting may mean that your liver or pancreas is
205 being damaged. A few patients have lung problems (such as pneumonia
206 inflammation of the lung tissue), and inflammation of the kidney. If you are short
207 of breath, coughing, or have severe stomach or back pains or a fever, you should
208 call your doctor right away.
- 209 • **Thyroid problems.** Some patients develop changes in the function of their
210 thyroid. Symptoms of thyroid changes include the inability to concentrate, feeling
211 cold or hot all the time, a change in your weight and changes to your skin.
- 212 • **New or worsening autoimmune disease.** Some patients taking INTRON A
213 develop autoimmune diseases (a condition where the body's immune cells attack
214 other cells or organs in the body), including rheumatoid arthritis, systemic lupus
215 erythematosus, sarcoidosis, and psoriasis. In some patients who already have
216 an autoimmune disease, the disease may worsen while on INTRON A.

217

218 Common but less serious side effects include:

219

- 220 • **Flu-like symptoms.** Most patients who take INTRON A have "flu-like"
221 symptoms (headache, muscle aches, tiredness, and fever) that usually lessen
222 after the first few weeks of therapy. You can reduce some of these symptoms by
223 injecting your INTRON A dose at bedtime. Over-the-counter pain and fever
224 medications can be used to prevent or reduce the fever and headache. If your
225 fever does not go away you should tell your doctor.
- 226 • **Extreme fatigue (tiredness).** Many patients become extremely tired while on
227 INTRON A.
- 228 • **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.
- 229 • **Blood sugar problems.** Some patients develop problems with the way their
230 body controls their blood sugar and may develop high blood sugar or diabetes.
- 231 • **Skin reactions.** Redness, swelling, and itching are common at the site of
232 injection. If after several days these symptoms do not disappear, contact your
233 doctor. You may get a rash during therapy. If this occurs, your doctor may
234 recommend medicine to treat the rash.
- 235 • **Hair thinning.** Hair thinning is common during INTRON A treatment. Hair loss
236 stops and hair growth returns after therapy is stopped.

237

238 These are not all the side effects of INTRON A or INTRON A/REBETOL combination
239 therapy. Your healthcare provider can give you a more complete list.

240

241 **General advice about prescription medicines**

242 Medicines are sometimes prescribed for purposes other than those listed in a
243 Medication Guide. If you have any concerns about the INTRON A product, ask your
244 healthcare provider. Your healthcare provider can give you additional information
245 about INTRON A. Do not use INTRON A for a condition for which it was not
246 prescribed. Do not share this medication with other people.

247

248 This Medication Guide has been approved by the U.S. Food and Drug
249 Administration.

250

251 Manufactured by: Schering Corporation Kenilworth, NJ 07033 USA

252

253 Issued: XX/XX

254

255 Instructional leaflet and video are available through your doctor.

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257 *Novofine is a registered trademark of Novo Nordisk

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260 Rev. 11/03

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262 **Medication Guide Appendix: Instructions for Preparing and Giving a Dose of**
263 **INTRON A Multidose Pen**

264

265 The INTRON A Solution for Injection multidose pen is a pre-filled, multidose pen that
266 contains six doses of either 3, 5, or 10 million international units (MIU) of INTRON A.
267 The multidose pen can also be used for different doses if your healthcare provider
268 wants you to increase or decrease your dose.

269

270 The multidose pen can provide between 3 to 12 doses depending upon the dose
271 your healthcare provider tells you to use. The multidose pen prescribed for you by
272 your healthcare provider will be one of the following:

273

- 274 • 3 Million International Units (MIU) with a brown push button and a brown color-
275 coding strip. The different doses that it can deliver are 1.5 MIU, 3.0 MIU, 4.5
276 MIU, and 6.0 MIU. Six MIU is the maximum dose that this pen can deliver at one
277 time.
- 278 • 5 Million International Units (MIU) with a light blue push button and a light blue
279 color-coding strip. The different doses that it can deliver are 2.5 MIU, 5.0 MIU,
280 7.5 MIU, and 10.0 MIU. Ten MIU is the maximum dose that this pen can deliver
281 at one time.
- 282 • 10 Million International Units (MIU) with a pink push button and a pink color-
283 coding strip. The different doses that it can deliver are 5.0 MIU, 10.0 MIU, 15.0
284 MIU, and 20.0 MIU. Twenty MIU is the maximum dose that this pen can deliver
285 at one time.

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Make sure that you have the correct INTRON A multidose pen as prescribed by your healthcare provider.

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Description of your INTRON A multidose pen

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- The INTRON A multidose pen should **ONLY** be used with **Novofine*** needles. These are the needles that come packaged with the pen. If you use other needles the pen may not work properly and you could get the wrong dose of INTRON A.

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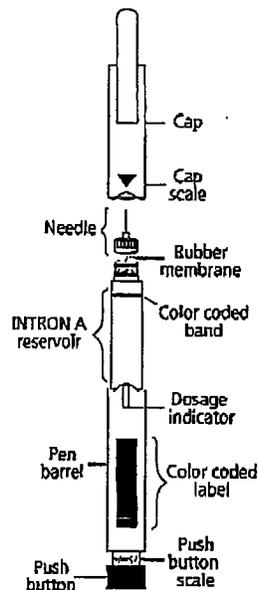
The two diagrams below show all the different parts of the INTRON A multidose pen and the Novofine needle. The parts of the pen you need to become familiar with are:

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INTRON A Pen



Novofine Needle Assembly



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- The **color-coded push button and push button scale**. These are located at the bottom of the pen when it is held with the cap side up. This tells you the dose that has been set.

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- The **color coding band**. This is located on the INTRON A reservoir. The band lets you know the dose that you are using. The 3 MIU INTRON A multidose pen has a brown push button, a brown color coding band and color coded label. The 5 MIU INTRON A multidose pen has a light blue push button, a light blue color coding band and color coded label. The 10 MIU INTRON A multidose pen has a pink push button, a pink color coding band and color coded label.

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- The **cap**. The cap is used for setting the dose and storing the pen. You will not be able to set the dose or completely close the pen unless you line up the **triangle on the cap scale** with the **dosage indicator on the barrel**.

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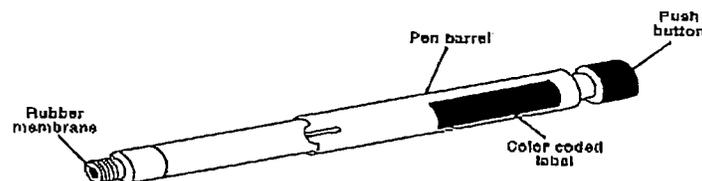
To avoid the possible transmission of disease, do not allow anyone else to use your multidose pen.

Storing INTRON A Solution Multidose Pen for Injection

INTRON A Solution Multidose Pen for Injection should be stored in the refrigerator between 2° and 8°C (36° and 46°F). Discard any unused INTRON A pen remaining after one month. **DO NOT FREEZE.**

How do I Prepare for an injection using the INTRON A multidose pen?

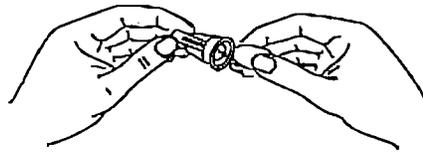
1. Find a well-lit, clean, flat working surface such as a table. Collect the supplies you will need for an injection:
 - The INTRON A multidose pen
 - Two alcohol swabs
 - A cotton ball or gauze
 - A puncture-proof disposable container
2. Before removing the multidose pen from the carton, check the date printed on the carton to make sure that the expiration date has not passed. Do not use if the expiration date has passed.
3. Wash your hands with soap and warm water. It is important to keep your work area, your hands and injection site clean to minimize the risk of infection.



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4. Remove the multidose pen from the carton. Pull the cap off the pen and wipe the rubber membrane with one alcohol swab.
5. Check the solution inside the pen. The solution should be clear and colorless, without particles. Do not use the INTRON A if the medicine is cloudy, has particles, or is any color besides clear and colorless.
6. Remove the paper backing from the Novofine needle by pulling the paper tab. You will see the back of the needle once the paper tab is removed.

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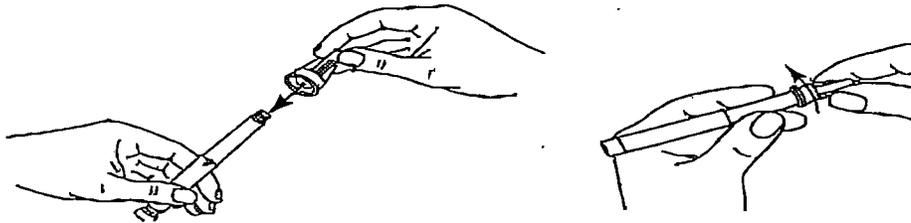
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7. Keep the needle in its outer clear needle cap and gently push the Novofine needle straight into the pen's rubber membrane you just cleaned. Screw the needle onto the INTRON A multidose pen by turning it clockwise.



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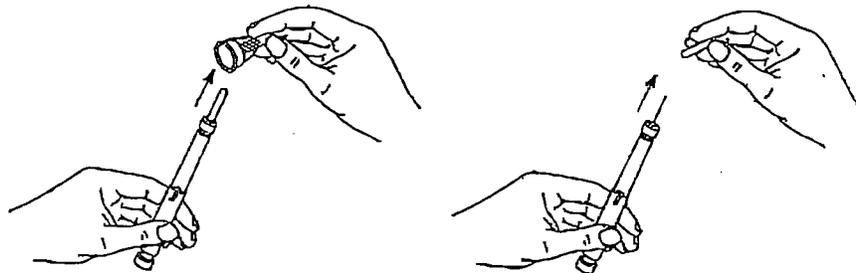
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8. With the needle facing up, pull off the outer clear needle cap and set the outer needle cap down on your flat work surface for later use. Next, carefully pull off the white inner needle cap. The needle will now be exposed.



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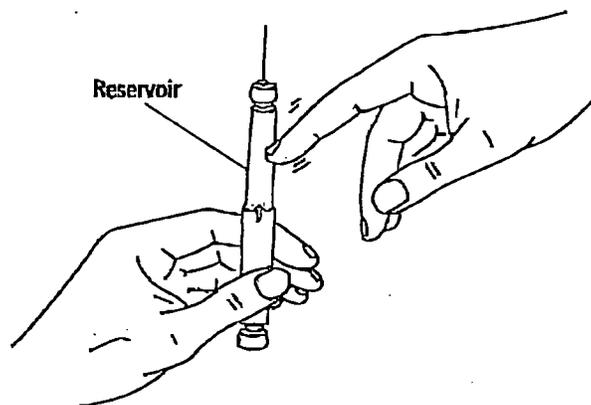
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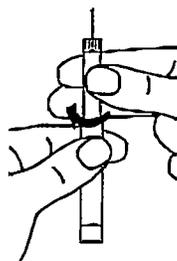
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9. Keep the needle facing up and remove any air bubbles that may be in the reservoir by tapping the reservoir with your finger. If you have any air bubbles, they will rise to the top of the reservoir.



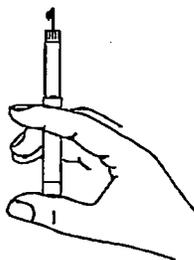
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10. Hold the pen by the barrel and turn the INTRON A reservoir clockwise until you feel it click into place.



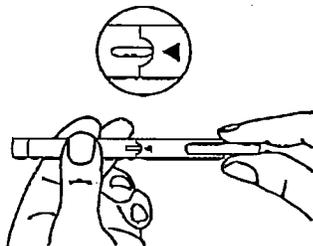
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11. Keep the needle facing up and press the push button all the way up. A drop of INTRON A solution should come out of the tip of the needle.



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12. If you do not see a drop of INTRON A solution, repeat steps 7, 8, and 9 until a drop comes out of the tip of the needle.
13. Place the cap back on the INTRON A multidose pen. Make sure you line up the black triangle on the pen cap with the dosage indicator on the pen barrel. The pen is now ready to set the dose.



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Setting the Dose Prescribed by Your Doctor

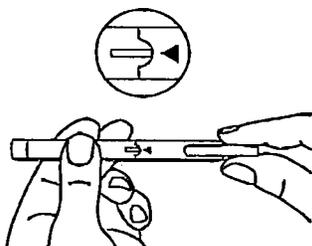
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14. Hold the pen horizontally in the middle of the pen barrel so the push button can move freely. With the other hand, hold the multidose pen cap.

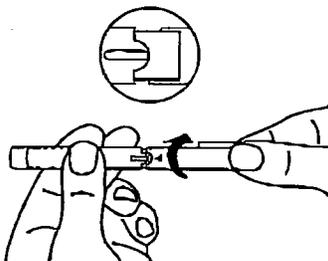
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15. Set the dose prescribed by your healthcare provider by turning the cap clockwise. With each clockwise turn, the push button will start to rise and you will see the push button scale. Do not use force to turn the pen cap or you may damage the pen.

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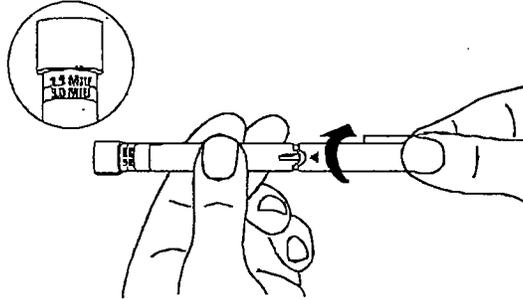
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- To set a 3.0 MIU dose using the 3 MIU multidose pen, turn the cap 2 full turns (10 clicks) = 3.0 MIU.

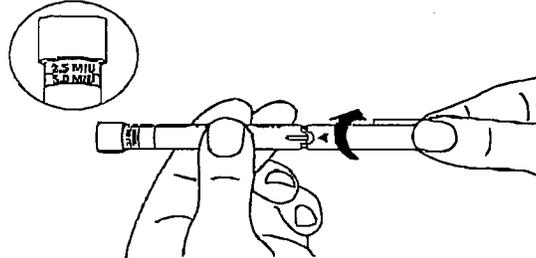
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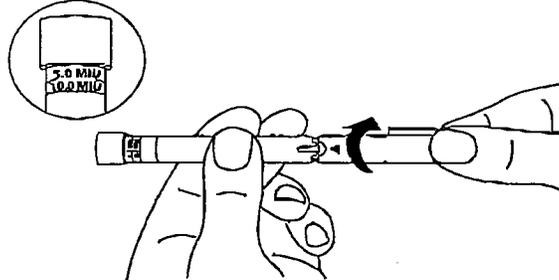
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- 414 • To set a 5 MIU dose using the 5 MIU multidose pen, turn the cap 2 full turns
415 (10 clicks) = 5.0 MIU.



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- 418 • To set a 10 MIU dose using the 10 MIU multidose pen, turn the cap 2 full
419 turns (10 clicks) = 10.0 MIU.



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- 423 16. After each complete turn, make sure the triangle on the cap is lined up with the
424 dosage indicator on the pen barrel.
425

426

427 **IF YOUR HEALTHCARE PROVIDER HAS PRESCRIBED A DOSE OTHER THAN**
428 **3.0, 5.0, OR 10.0 MIU, THE DOSE CAN BE SET BY TURNING THE CAP AS**
429 **MANY TIMES AS SHOWN BELOW:**

430

A dose prescribed other than 3.0 MIU from the 3 MIU multidose pen

431

1 full turn (5 clicks) = 1.5 MIU

432

3 full turns (15 clicks) = 4.5 MIU

433

4 full turns (20 clicks) = 6.0 MIU

434

435

A dose prescribed other than 5.0 MIU from the 5 MIU multidose pen

436

1 full turn (5 clicks) = 2.5 MIU

437

3 full turns (15 clicks) = 7.5 MIU

438

4 full turns (20 clicks) = 10.0 MIU

439

440

A dose prescribed other than 10.0 MIU from the 10 MIU multidose pen

441

1 full turn (5 clicks) = 5.0 MIU

442

3 full turns (15 clicks) = 15.0 MIU

443

4 full turns (20 clicks) = 20.0 MIU

444

445

17. Check the push button scale to make sure you have set the correct dose.

446

447

18. If you have set a wrong dose, turn the cap back (counterclockwise) as far as you can until the push button is all the way in and the push button scale is completely covered, then begin at step 13 again.

448

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451

19. Gently warm the INTRON A Solution for Injection by slowly rolling the capped multidose pen in the palms of your hands for about one minute. DO NOT SHAKE.

452

453

454

455

20. Place the multidose pen on your flat work surface until you are ready to inject INTRON A.

456

457

458

Choosing an Injection Site

459

460

You should inject a dose of INTRON A subcutaneously (under the skin). If it is too difficult for you to inject, ask someone who has been trained to give injections to help you.

461

462

463

464

The best sites for injection are areas on your body with a layer of fat between skin and muscle such as:

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- the front of the middle thighs
- the outer area of the upper arms
- the abdomen, except around the navel

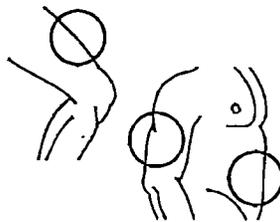
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You should use a different site each time you inject INTRON A to avoid soreness at any one site. Do not inject INTRON A into an area where the skin is irritated, red, bruised, infected or has scars, stretch marks or lumps.

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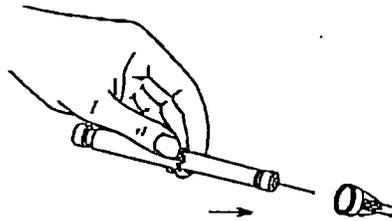
Injecting Your Dose of INTRON A

480

- 481 1. Clean the injection site with a new alcohol swab.
482
483 2. Pick up the multidose pen from your flat work surface and remove the cap from
484 the needle.
485
486 3. With one hand, pinch a fold of the skin at the cleaned injection site.
487
488 4. With the other hand, hold the multidose pen (like a pencil) at a **45 degree angle**
489 to the skin. With a quick "dart-like" motion to push the needle into the skin.
490
491



- 492
493
494 5. After the needle is in, remove the hand used to pinch the skin and use it to hold
495 the pen barrel. Pull the plunger back slightly. If blood comes into the pen
496 reservoir, the needle has entered a blood vessel. **Do not inject INTRON A.**
497 Withdraw the needle and discard the used multi-dose pen in the puncture-proof
498 container. Contact your healthcare provider. Repeat the steps to prepare for an
499 injection.
500
501 6. If no blood is present in the pen reservoir, inject the medicine by gently pressing
502 the push button all the way down
503
504 7. Leave the needle in place for a few seconds while holding down the push button.
505
506 8. Slowly release the push button and pull the needle out of the skin.
507
508 9. Place a cotton ball or gauze over the injection site and press for several
509 seconds. Do not massage the injection site. If there is bleeding, cover the
510 injection site with a bandage.
511
512 10. It is important to check your injection site approximately two hours after your
513 injection for redness, swelling, or tenderness. These are signs of inflammation
514 that you may need to talk to your healthcare provider about if they do not go
515 away
516
517 **Removing the needle from the multidose pen**
518
519 11. Using a scooping motion and carefully replace the outer clear needle cap (like
520 capping a pen).
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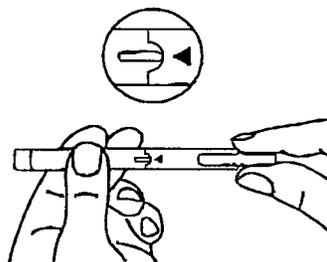
12. Once capped remove the needle by holding the clear outer needle cap with one hand and holding the pen barrel with the other hand, turning counterclockwise.



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13. Carefully lift the needle off the pen and discard the capped needle. See *How should I dispose of materials used to inject INTRON A?*

14. Replace the pen cap over the pen reservoir so that the black triangle is lined up with the dosage indicator.



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Storing INTRON A Solution Multidose Pen for Injection

INTRON A Solution Multidose Pen for Injection should be stored in the refrigerator between 2° and 8°C (36° and 46°F). **DO NOT FREEZE.** Discard any unused INTRON A pen remaining after one month.

How should I dispose of material used to inject INTRON A?

545 There may be special state and local laws for disposal of used needles and
546 multidose pens. Your healthcare provider should provide you with instructions on
547 how to properly dispose of your used needles and multidose pens. Always follow
548 these instructions. The instructions below should be used as a general guide for
549 proper disposal.

550

551 • The needles should never be reused.

552

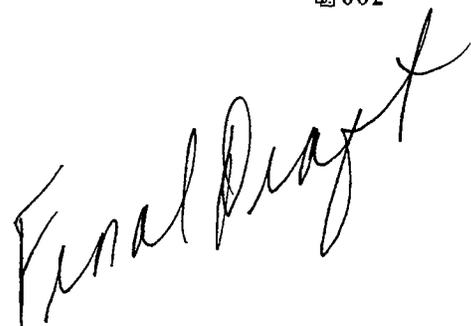
553 • Place all used needles and multidose pens in a puncture-proof disposable
554 container that is available through your pharmacy or healthcare provider. You
555 may use a hard plastic container with a screw-on cap (like a laundry detergent
556 container). DO NOT use glass or clear plastic containers for disposal of needles.

557

558 • The container should be clearly labeled as "USED NEEDLES AND MULTIDOSE
559 PENS." When the container is about two-thirds full, dispose of the container as
560 instruction by your healthcare provider. DO NOT throw the container in your
561 household trash. DO NOT recycle.

562

563 • Always keep the container out of the reach of children.



1 F-XXXXXXXX

2

3 **MEDICATION GUIDE**

4

5 **INTRON® A**

6 (Interferon alfa-2b, recombinant)

7

8 **Including appendix with instructions for using INTRON A Solution for Injection**

9

10 Read this Medication Guide carefully before you start to take INTRON A (In-tron
11 aye) for Injection alone or INTRON A in combination with REBETOL (REB-eh-tole)
12 (ribavirin, USP) Capsules. Read the Medication Guide each time you refill your
13 prescription because there may be new information. The information in this
14 Medication Guide does not take the place of talking with your healthcare provider.

15

16

17 If you are taking INTRON A and REBETOL combination therapy, also read the
18 medication guide for REBETOL (ribavirin, USP) Capsules.

19

20 **What is the most important information I should know about INTRON A?**

21

22 INTRON A is a treatment for some people who have hairy cell leukemia, malignant
23 melanoma, follicular lymphoma, AIDS-related Kaposi's sarcoma, chronic hepatitis B,
24 chronic hepatitis C and condylomata acuminata. If you have chronic hepatitis C,
25 your healthcare provider may prescribe INTRON A in combination with REBETOL.
26 INTRON A used by itself or with REBETOL can help you, but can also have serious
27 side effects and may death in rare cases. Before starting treatment, you should talk
28 to your healthcare provider about the possible benefits and possible side effects of
29 INTRON A alone or in combination with REBETOL, to decide if this treatment is right
30 for you. While taking INTRON A alone or in combination with REBETOL, you need
31 to see a healthcare provider regularly for medical examinations and lab tests to
32 make sure the treatment is working and to check for side effects.

33

34 **You should call your doctor immediately if you develop any of these** 35 **conditions while taking INTRON A:**

- 36 • You become pregnant or if you are a male and your female partner becomes
37 pregnant
 - 38 • New or worsening mental health problems such as thoughts about hurting or
39 killing yourself or others
 - 40 • Decreased vision
 - 41 • Trouble breathing or chest pain
 - 42 • Severe stomach or lower back pain
 - 43 • Bloody diarrhea or bloody bowel movements
 - 44 • High fever
 - 45 • Easy bruising or bleeding
- 46

47 The most serious possible side effects of INTRON A include:

48

49 **RISK TO PREGNANCY.** Combination INTRON A and REBETOL therapy can
50 cause death, serious birth defects or other harm to your unborn child. If you
51 are pregnant, you or your male partner must not take INTRON A and REBETOL
52 combination therapy. You must not become pregnant while either you or your
53 partner are taking the combination of INTRON A and REBETOL and for 6
54 months after you stop taking the combination. If you are a woman of
55 childbearing age you must have negative pregnancy tests immediately before
56 starting treatment, during treatment and for 6 months after you have stopped
57 treatment. You should use two forms of birth control during and for 6 months
58 after you have stopped treatment. If you are a man taking INTRON A/REBETOL
59 combination therapy, one of the two forms of birth controls should be a
60 condom. You must use birth control even if you believe that you are not fertile
61 or that your fertility is low. You should talk to your doctor about birth control
62 for you and your partner. If you or your partner becomes pregnant while either
63 of you is being treated or within 6 months of stopping treatment tell your
64 doctor right away.

65
66 **Mental health problems and suicide.** INTRON A may cause patients to develop
67 mood or behavioral problems. These can include irritability (getting easily upset)
68 and depression (feeling low, feeling bad about yourself, or feeling hopeless). Some
69 patients may have aggressive behavior. Former drug addicts may fall back into drug
70 addiction or overdose. Some patients think about hurting or killing themselves or
71 other people. Some patients have killed themselves (suicide) or hurt themselves or
72 others. You must tell your doctor if you are being treated for a mental illness or had
73 treatment in the past for any mental illness, including depression and suicidal
74 behavior. You should also tell your doctor if you have ever been addicted to drugs
75 or alcohol.

76
77 **Eye problems.** If you notice any changes in your eyesight such as difficulty seeing,
78 it could mean that your eyes are being affected, so you should call your doctor right
79 away.

80
81 **Heart problems.** Some patients taking INTRON A may develop problems with their
82 heart, including low blood pressure, fast heart rate, and very rarely, heart attacks.
83 Tell your doctor if you have had any heart problems in the past.

84
85 **Blood problems.** INTRON A commonly lowers two types of blood cells (white
86 blood cells and platelets). In some patients, these blood counts may fall to
87 dangerously low levels. If your blood cell counts become very low, you could get
88 infections or have bleeding problems.

89
90 If you are taking INTRON A and REBETOL combination therapy, REBETOL can
91 cause a drop in your number of red blood cells (anemia). A very low red blood cell
92 count can be dangerous especially if you have heart or breathing problems.
93 For other possible side effects of INTRON A. see "What are the possible side
94 effects of INTRON A?" in this Medication Guide.

95 What is INTRON A?

96

97 The INTRON A product contains a man-made protein called interferon. Interferon is
98 a protein that is part of the body's immune system that "interferes" with the growth of
99 viruses or cancer cells.

100

101 It is not known if INTRON A or INTRON A/REBETOL combination therapy can cure
102 hepatitis B or C (permanently eliminate the virus) or if it can prevent liver failure or
103 liver cancer that is caused by hepatitis B or C infection.

104

105 It is also not known if INTRON A or INTRON A/REBETOL combination therapy will
106 prevent one infected person from infecting another person with hepatitis B or C.

107

108 Who should not take INTRON A?

109

110 Do not take the INTRON A alone or in combination with REBETOL if you:

111

- 112 • are pregnant, planning to get pregnant, or breast-feeding.
- 113 • are a male patient on combination therapy and have a female sexual partner who
114 is pregnant or plans to become pregnant while you are being treated with
115 REBETOL or during the 6 months after your treatment has ended.
- 116 • have autoimmune hepatitis (hepatitis caused by your immune system attacking
117 your liver) or unstable liver disease (yellowing of the skin and eyes, swelling of
118 the abdomen).
- 119 • had an allergic reaction to another alpha interferon or ribavirin or are allergic to
120 any of the ingredients in INTRON A or REBETOL.

121

122 **If you have any of the following conditions or serious medical problems, tell**
123 **your doctor before taking INTRON A alone or in combination with REBETOL:**

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- 124 • depression or anxiety
- 125 • eye problems
- 126 • sleep problems
- 127 • high blood pressure
- 128 • previous heart attack, or other heart problems
- 129 • liver problems (other than hepatitis B or C)
- 130 • any kind of autoimmune disease (where the body's immune system attacks the
131 body's own cells), such as psoriasis, sarcoidosis, systemic lupus erythematosus,
132 rheumatoid arthritis
- 133 • thyroid problems
- 134 • diabetes
- 135 • colitis (inflammation of the bowels)
- 136 • cancer
- 137 • hepatitis B or C infection
- 138 • HIV infection (the virus that causes AIDS)
- 139 • kidney problems
- 140 • bleeding problems
- 141 • alcoholism

- 142 • drug abuse or addiction
- 143 • body organ transplant and are taking medicine that keeps your body from
- 144 rejecting your transplant (suppresses your immune system).
- 145 • high blood triglycerides (fat particles normally found in you blood)

146

147 How should I take INTRON A?

148

149 To get the most benefit from this medicine, it is important that you take INTRON A
150 exactly as your doctor tells you. Your doctor will decide your dose of INTRON A and
151 how often you will take it. Do not take more than your prescribed dose. INTRON A is
152 given as an injection either under the skin (subcutaneous) or into a muscle
153 (intramuscular). You should be completely comfortable with how to prepare and
154 measure your dose of INTRON A and how to inject yourself before you use INTRON
155 A for the first time. Your healthcare provider will train you on how to use and inject
156 INTRON A properly.

157

158 INTRON A comes in different strengths and different forms (a powder in a vial, a
159 solution in a vial and a multidose pen). Your doctor will determine which form is best
160 for you. The instructions for giving a dose of INTRON A are at the end of this leaflet.

161

162 If you miss a dose of INTRON A, take the missed dose as soon as possible during
163 the same day or the next day, then continue on your regular dosing schedule. If
164 several days go by after you miss a dose, check with your doctor to see what to do.
165 **Do not double your next dose** or take more than your prescribed dose without
166 talking to your doctor. Call your doctor right away if you take more than your
167 prescribed dose. Your doctor may wish to examine you more closely and take blood
168 for testing.

169

170 If you are taking INTRON A in combination with REBETOL, you should also read the
171 Medication Guide for REBETOL (ribavirin, USP) for more information about side
172 effects and how to take REBETOL. **REBETOL capsules should be taken twice a**
173 **day with food.** Taking REBETOL with food helps your body take up more of the
174 medicine. Taking REBETOL at the same time of day every day will help keep the
175 amount of medicine in your body at a steady level. This can help your doctor decide
176 how your treatment is working and how to change the dose number of REBETOL
177 ~~capsules~~ you take if you have side effects. If you miss a dose of REBETOL, take the
178 missed dose as soon as possible during the same day. If an entire day has passed,
179 check with your doctor about what to do. **Do not double your next dose.**

180 You must see your doctor on a regular basis for blood tests so your doctor can
181 check how the treatment is working for you and to check for side effects.

182

183 Tell your doctor if you are taking or planning to take other prescription or non-
184 prescription medicines, including vitamin and mineral supplements and herbal
185 medicines.

186

187 What should I avoid while taking INTRON A?

- 188 • Avoid becoming pregnant while taking the INTRON A. INTRON A alone and
- 189 INTRON A taken in combination with REBETOL may harm your unborn child or

190 cause you to lose your baby (miscarry). If you or your partner becomes pregnant
191 during treatment or during the 6 months after treatment with INTRON
192 A/REBETOL combination therapy, immediately report the pregnancy to your
193 doctor. Your doctor will make decisions about your treatment.
194

- 195 • Do not breast-feed your baby while taking INTRON A.
196

197 What are the possible side effects of INTRON A? 198

199 Possible, serious side effects include:
200

- 201 • **Risk to pregnancy, mental health problems, including suicide, blood**
202 **problems, and heart problems and eye problems.** see *"What is the most*
203 *important information I should know about INTRON A?"*
- 204 • **Other body organ problems.** Certain symptoms like severe pain in the middle
205 of your body, nausea, and vomiting may mean that your liver or pancreas is
206 being damaged. A few patients have lung problems such as pneumonia
207 (inflammation of the lung tissue), and inflammation of the kidney. If you are short
208 of breath, coughing or have severe stomach or back pains or a fever, you should
209 call your doctor right away.
- 210 • **Thyroid problems.** Some patients develop changes in the function of their
211 thyroid. Symptoms of thyroid changes include the inability to concentrate, feeling
212 cold or hot all the time, a change in your weight and changes to your skin.
- 213 • **New or worsening autoimmune disease.** Some patients taking INTRON A
214 develop autoimmune diseases (a condition where the body's immune cells attack
215 other cells or organs in the body), including rheumatoid arthritis, systemic lupus
216 erythematosus, sarcoidosis, and psoriasis. In some patients who already have
217 an autoimmune disease, the disease may worsen while on INTRON A.
218

219 Common but less serious side effects include:
220

- 221 • **Flu-like symptoms.** Most patients who take INTRON A have "flu-like"
222 symptoms (headache, muscle aches, tiredness, and fever) that usually lessen
223 after the first few weeks of therapy. You can reduce some of these symptoms by
224 injecting your INTRON A dose at bedtime. Over-the-counter pain and fever
225 medications can be used to prevent or reduce the fever and headache. If your
226 fever does not go away you should tell your doctor.
- 227 • **Extreme fatigue (tiredness).** Many patients become extremely tired while on
228 INTRON A.
- 229 • **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.
- 230 • **Blood sugar problems.** Some patients develop problems with the way their
231 body controls their blood sugar and may develop high blood sugar or diabetes.
- 232 • **Skin reactions.** Redness, swelling, and itching are common at the site of
233 injection. If after several days these symptoms do not disappear, contact your
234 doctor. You may get a rash during therapy. If this occurs, your doctor may
235 recommend medicine to treat the rash.
236

- 237 • **Hair thinning.** Hair thinning is common during INTRON A treatment. Hair loss
238 stops and hair growth returns after therapy is stopped.
239

240 These are not all the side effects of INTRON A or INTRON A/REBETOL combination
241 therapy. Your healthcare provider can give you a more complete list.
242

243 **General advice about prescription medicines**

244 Medicines are sometimes prescribed for purposes other than those listed in a
245 Medication Guide. If you have any concerns about the INTRON A product, ask
246 healthcare provider. Your health care provider can give you additional information
247 about INTRON A. Do not use INTRON A for a condition for which it was not
248 prescribed. Do not share this medication with other people.
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251 This Medication Guide has been approved by the U.S. Food and Drug
252 Administration.
253

254 Manufactured by: Schering Corporation Kenilworth, NJ 07033 USA
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256 Issued: XX/XX
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258 *Safety-Lok is a registered trademark of Becton Dickinson
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260 Copyright © 1996, 2001, Schering Corporation.
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263 **Medication Guide Appendix: Instructions for Preparing and Giving a Dose of** 264 **INTRON A Solution for Injection** 265 266

- 267 • INTRON A medication has been supplied to you in a liquid form in a vial.
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269 **The INTRON A Solution for Injection may be supplied to you as either:**
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- 271 • **INTRON A Solution in a Pak-10 (10 million IU) package.** This package
272 contain 6 single-use INTRON A vials of solution, 6 single-use disposable Safety-
273 Lok* syringes, and 12 alcohol swabs.
274

- 275 • **INTRON A Solution 18 million IU and 25 million IU multidose vial.** These
276 packages contain 1 vial of INTRON A solution. Syringes are not supplied to you.
277 Talk to your healthcare provider about what syringes you should use.
278

279 **Storing INTRON A Solution for Injection**

280 INTRON A Solution for Injection should be stored in the refrigerator between 2° and
281 8°C (36° and 46°F). **DO NOT FREEZE.** If you are using the Pak-10, 10 Million IU
282 single use vials discard any unused INTRON A solution remaining after use. If you

283 are using the 18 or 25 million IU multidose vials discard any unused INTRON A
284 solution remaining after one month.

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286 Preparing a Dose of INTRON A Solution for Injection

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288 1. Find a well lit, clean, flat working surface such as a table. Collect the supplies
289 you will need for an injection:

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291

- A vial of INTRON A solution

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- A single-use disposable syringe Safety-Lok* syringe provided in the "Pak-10"
293 only, or a syringe you have obtained for use with the multi-use vials

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- A cotton ball or gauze

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- Two alcohol swabs

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- A puncture-proof disposable container

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298 2. Before removing contents from the carton, check the expiration date printed on
299 the carton to make sure that the expiration date has not passed. Do not use if
300 the expiration date has passed.

301

302 3. Wash your hands with soap and warm water. It is important to keep your work
303 area, your hands and injection site clean to minimize the risk of infection.

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305 4. If you are using the Pak-10 packages remove one vial of INTRON A solution, one
306 Safety-Lok* syringe and two alcohol swabs from the "Pak".

307

308 5. Check the vial of INTRON. The solution should be clear and colorless, without
309 particles. Do not use the vial of INTRON A if the medicine is cloudy, has
310 particles or is any color beside clear and colorless.

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312 6. Remove the protective plastic caps from the top of the INTRON A vial. Clean
313 the rubber stopper on the top of the INTRON A vial with an alcohol swab.

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315 7. Gently warm the INTRON A solution by slowly rolling the vial in the palms of your
316 hands for about one minute. **DO NOT SHAKE.**

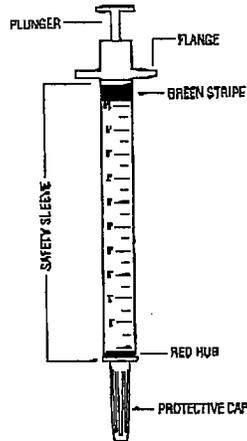
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318 8. If you are using the Pak-10 packages, remove the protective wrapper from the
319 Safety-Lok* syringe. The Safety-Lok* syringe has a clear safety sleeve. The
safety sleeve should fit snugly against the flange (finger grip area of syringe) and
only be moved over the needle when ready for disposal.

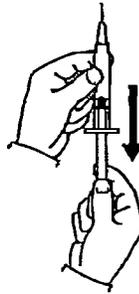
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317 If you are using the multidose vials, open the package for the syringe you are using
318 and if it does not have a needle attached, then attach one of the needles you have
319 obtained to the syringe.

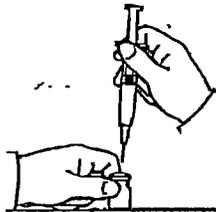
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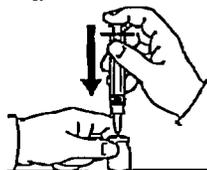
9. Remove the protective cap from the needle of the syringe. Fill the syringe with air by pulling the plunger back to the mark on the syringe that matches the dose as prescribed by your healthcare provider.

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10. Hold the INTRON A vial solution for injection on your flat working surface without touching the cleaned rubber stopper with your hands.

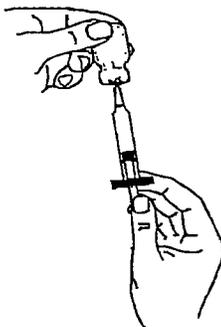
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11. Insert the needle straight down through the middle of the rubber stopper of the vial containing the INTRON A solution. Slowly inject all the air from the syringe into the air space above the solution.

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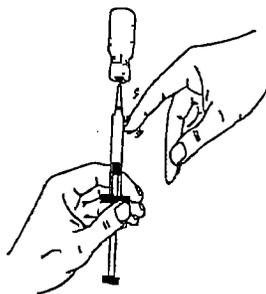
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12. Keep the needle in the vial and turn the vial upside down. Make sure the tip of the needle is in the INTRON A solution. Slowly pull the plunger back to fill the syringe with INTRON A solution to the number (mL or cc) as prescribed by your healthcare provider.



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13. With the needle in the vial, check the syringe for air bubbles. If there are any air bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to remove the air bubbles. If you push solution back into the vial, slowly pull back on the plunger to again draw the correct dose as prescribed by your healthcare provider.



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14. Do not remove the needle from the vial. Lay the vial and syringe on its side on your flat work surface until you are ready to inject the INTRON A solution.

Choosing an Injection site

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Based on your treatment, your healthcare provider will tell you if you should inject a dose of INTRON A subcutaneously (under the skin) or intramuscularly (into the muscle). If it is too difficult for you to inject, ask someone who has been trained to give injections to help you.

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FOR SUBCUTANEOUS INJECTION

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The best sites for injection are areas on your body with a layer of fat between skin and muscle such as:

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- the front of your middle thighs
- the outer area of your upper arms
- the abdomen, except around the navel

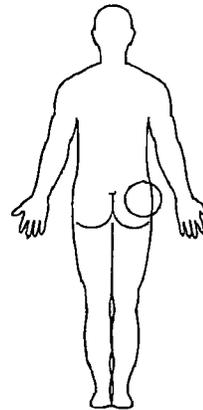
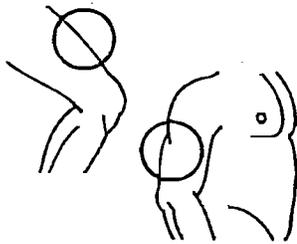


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FOR INTRAMUSCULAR INJECTION

The best sites for injection into your muscle are:

- the front of the middle thighs
- the uppers arms
- the upper outer areas of the buttocks



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You should use a different site each time you inject INTRON A to avoid soreness at any one site. Do not inject INTRON A into an area where the skin is irritated, red, bruised, infected or has scars, stretch marks or lumps.

Injecting the Dose of INTRON A

1. Clean the injection site with a new alcohol swab.
2. Pick up the vial and syringe from your flat work surface. Remove the syringe and needle from the vial. Hold the syringe in the hand that you will use to inject INTRON A. Do not touch the needle or allow it to touch the work

421 surface. If you are using a Safety-Lok* syringe, make sure the safety sleeve
422 is pushed against the syringe flange so that the needle is fully exposed.

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3. With your free hand, pinch a fold of the skin at the cleaned injection site.

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FOR SUBCUTANEOUS INJECTION:

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- 4b. Hold the syringe (like a pencil) at a **45-degree angle** to the skin. With a quick
429 "dart-like" motion, push the needle into the skin.

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FOR INTRAMUSCULAR INJECTION:

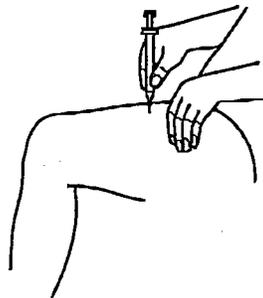
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- 4b. Hold the syringe (like a pencil) at a **90-degree angle** to the skin. With a
448 quick "dart-like" motion, push the needle into the muscle.

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5. After the needle is in, remove the hand used to pinch the skin and use it to hold
454 the syringe barrel. Pull the plunger back slightly. If blood comes into the syringe,
455 the needle has entered a blood vessel. **Do not inject INTRON A.** Withdraw the
456 needle and discard the syringe in the puncture-proof container. *See "How should
457 I dispose of materials used to inject INTRON A?"*) Prepare a new dose of
458 INTRON A and prepare a new injection site.

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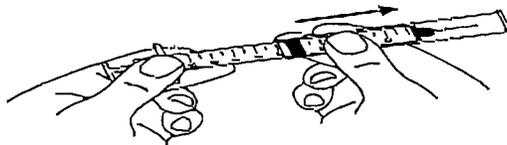
6. If no blood is present in the syringe, inject the medicine by gently pushing the
plunger all the way down until the syringe is empty.

- 462 7. When the syringe is empty, pull the needle out of the skin and place a cotton ball
463 or gauze over the injection site and press for several seconds. Do not massage
464 the injection site. If there is bleeding, cover the injection site with a bandage.
- 465 8. Dispose of syringe and needle. See "How should I dispose of materials used to
466 inject INTRON A?"
- 467 9. If you are using a single-use vial (10 million IU), discard the INTRON A vial and
468 any remaining solution after use. If you are using a multidose vial (18 million IU
469 or 25 million IU) and there is enough solution left in the vial for another dose,
470 refrigerate the INTRON A vial after use. Discard any unused INTRON A solution
471 remaining after one month.
- 472 10. It is important to check your injection site approximately two hours after your
473 injection for redness, swelling, or tenderness. These are signs of inflammation
474 that you may need to talk to your healthcare provider about if they do not go
475 away.

476 How should I dispose of materials used to inject INTRON A?

477 There may be special state and local laws for disposal of used needles and
478 syringes. Your healthcare provider should provide you with instructions on how to
479 properly dispose of your used syringes and needles. Always follow those
480 instructions. The instructions below should be used as a general guide for proper
481 disposal.

- 482
- 483 • **The needles and syringes should never be reused**
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 - 486 • **Disposing of the Safety-Lok* syringe.** To dispose of the Safety-Lok* syringe,
487 hold the flange of the syringe with one hand. Grasp the safety sleeve with your
488 free hand, sliding it completely over the needle. The green stripe on the safety
489 sleeve should cover the red hub of the needle and fit snugly.



- 493
- 494
 - 495 • Place all used needles and syringes in a puncture-proof disposable container
496 that is available through your pharmacy or healthcare provider. You may also use
497 a hard plastic container with a screw-on cap (like a laundry detergent container).
498 Do not use glass or clear plastic containers for disposal of needles and syringes.
 - 499 • The container used for the disposal of syringes, needles, and Safety-Lok*
500 syringes should be clearly labeled as "USED SYRINGES AND NEEDLES."

Page 13

- 501 When the container is almost full, tighten the lid. Tape the cap or lid to make
502 sure it does not come off. Dispose of the container as instructed by your
503 healthcare provider.
504 DO NOT throw the container in your household trash and DO NOT recycle.
505
506 • **Always keep the container out of reach of children.**