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**PRODUCT
INFORMATION**

INTRON® A
Interferon alfa-2b,
recombinant
For Injection

WARNING

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

DESCRIPTION

INTRON® A (Interferon alfa-2b) for intramuscular, subcutaneous, intralesional, or intravenous Injection is a purified sterile recombinant interferon product.

INTRON® A, recombinant for Injection has been classified as an alfa interferon and is a water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride at a concentration of 5 to 10 mg/L; the presence of this antibiotic is not detectable in the final product. The specific activity of Interferon alfa-2b, recombinant is approximately 2.6×10^8 IU/mg protein as measured by the HPLC assay.

Powder for Injection

Vial Strength Million IU	mL Diluent	Final Concentration after Reconstitution million IU/mL*	mg INTRON A† 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.

Prior to administration, the INTRON A Powder for Injection is to be reconstituted with the provided Diluent for INTRON A (Sterile Water for Injection, USP) (see **DOSAGE AND ADMINISTRATION**). INTRON A Powder for Injection is a white to cream-colored powder.

Solution Vials for Injection

		mg INTRON A†	
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Vial Strength	Concentration*	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 (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 (for a label strength of 25 million IU).

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Solution in Multidose Pens for Injection

Pen Strength	Concentration* Million IU/1.5ml	INTRON A Dose Delivered (6 doses, 0.2 mL each)	mg INTRON A [†] per 1.5 mL	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.

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

CLINICAL PHARMACOLOGY

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

Preclinical Pharmacology Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. *In vitro* studies demonstrated that these include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.



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

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

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

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

67 After intravenous administration, serum INTRON A concentrations peaked
68 (135 to 273 IU/mL) by the end of the 30-minute infusion, then declined at a slightly
69 more rapid rate than after intramuscular or subcutaneous drug administration,
70 becoming undetectable 4 hours after the infusion. The elimination half-life was
71 approximately 2 hours.

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

76 There are no pharmacokinetic data available for the intralesional route of
77 administration.

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

87 Serum anti-interferon neutralizing antibodies were detected in 7% (12/168) of
88 patients either during treatment or after completing 12 to 48 weeks of treatment with
89 3 million IU TIW of INTRON A therapy for chronic hepatitis C and in 13% (6/48) of
90 patients who received INTRON A therapy for chronic hepatitis B at 5 million IU QD
91 for 4 months, and in 3% (1/33) of patients treated at 10 million IU TIW. Serum anti-
92 interferon neutralizing antibodies were detected in 9% (5/53) of pediatric patients
93 who received INTRON A therapy for chronic hepatitis B at 6 million IU/m² TIW.
94 Among all chronic hepatitis B or C patients, pediatric and adults with detectable
95 serum neutralizing antibodies, the titers detected were low (22/24 with titers ≤1:40
96 and 2/24 with titers ≤1:160). The appearance of serum anti-interferon neutralizing
97 activity did not appear to affect safety or efficacy.



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

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

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

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

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138 **Malignant Melanoma** The safety and efficacy of INTRON A was evaluated as
139 adjuvant to surgical treatment in patients with melanoma who were free of disease
140 (post surgery) but at high risk for systemic recurrence. These included patients with
141 lesions of Breslow thickness >4 mm, or patients with lesions of any Breslow
142 thickness with primary or recurrent nodal involvement. In a randomized, controlled
143 trial in 280 patients, 143 patients received INTRON A therapy at 20 million IU/m²



144 intravenously five times per week for 4 weeks (induction phase) followed by 10
145 million IU/m² subcutaneously three times per week for 48 weeks (maintenance
146 phase). In the clinical trial, the median daily INTRON A dose administered to
147 patients was 19.1 million IU/m² during the induction phase and 9.1 million IU/m²
148 during the maintenance phase. INTRON A therapy was begun ≤56 days after
149 surgical resection. The remaining 137 patients were observed.

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

159
160 In a second study of 642 resected high-risk melanoma patients, subjects were
161 randomized equally to one of three groups: high-dose INTRON A therapy for 1 year
162 (same schedule as above), low-dose INTRON A therapy for 2 years (3 MU/d TIW
163 SC), and observation. Consistent with the earlier trial, high-dose INTRON A therapy
164 demonstrated an improvement in relapse-free survival (3-year estimated RFS 48%
165 vs. 41%; median RFS 2.4 vs. 1.6 years, p = not significant). Relapse-free survival in
166 the low-dose INTRON A arm was similar to that seen in the observation arm.
167 Neither high-dose nor low-dose INTRON A therapy showed a benefit in overall
168 survival as compared to observation in this study.

169
170 **Follicular Lymphoma** The safety and efficacy of INTRON A in conjunction with
171 CHVP, a combination chemotherapy regimen, was evaluated as initial treatment in
172 patients with clinically aggressive, large tumor burden, Stage III/IV follicular Non-
173 Hodgkin's Lymphoma. Large tumor burden was defined by the presence of any one
174 of the following: a nodal or extranodal tumor mass with a diameter of >7 cm;
175 involvement of at least three nodal sites (each with a diameter of >3 cm); systemic
176 symptoms; splenomegaly; serous effusion, orbital or epidural involvement; ureteral
177 compression; or leukemia.

178 In a randomized, controlled trial, 130 patients received CHVP therapy and
179 135 patients received CHVP therapy plus INTRON A therapy at 5 million IU
180 subcutaneously three times weekly for the duration of 18 months. CHVP
181 chemotherapy consisted of cyclophosphamide 600 mg/m², doxorubicin 25 mg/m²,
182 and teniposide (VM-26) 60 mg/m², administered intravenously on Day 1 and
183 prednisone at a daily dose of 40 mg/m² given orally on Days 1 to 5. Treatment
184 consisted of six CHVP cycles administered monthly, followed by an additional
185 6 cycles administered every 2 months for 1 year. Patients in both treatment groups
186 received a total of 12 CHVP cycles over 18 months.

187 The group receiving the combination of INTRON A therapy plus CHVP had a
188 significantly longer progression-free survival (2.9 years vs. 1.5 years, p=0.0001, Log
189 Rank test). After a median follow-up of 6.1 years, the median survival for patients

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

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

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

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

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

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

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

230 Another study involved 97 patients in whom three lesions were treated with
231 either an intralesional injection of 1.5 million IU of INTRON A per lesion followed by
232 a topical application of 25% podophyllin, or a topical application of 25% podophyllin
233 alone. Treatment was given once a week for 3 weeks. The combined treatment of
234 INTRON A and podophyllin was shown to be significantly more effective than
235 podophyllin alone, as determined by the number of patients whose lesions cleared.

236 This significant difference in response was evident after the second treatment (Week
237 3) and continued through 8 weeks posttreatment. At the time of the patient's best
238 response, 67% (33/49) of the INTRON A and podophyllin treated patients had all
239 three treated lesions clear while 42% (20/48) of the podophyllin treated patients had
240 all three clear ($p=0.003$).

241

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

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

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

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

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

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

273 For patients who received 30 million IU TIW, the median survival time was
274 longer in patients with CD4 >200 (30.7 months) than in patients with CD4 ≤200
275 (8.9 months). Among responders, the median survival time was 22.6 months vs.
276 9.7 months in nonresponders.

277 **Chronic Hepatitis C** The safety and efficacy of INTRON A in the treatment of
278 chronic hepatitis C was evaluated in 5 randomized clinical studies in which an
279 INTRON A dose of 3 million IU three times a week (TIW) was assessed. The initial
280 three studies were placebo-controlled trials that evaluated a 6-month (24-week)
281 course of therapy. In each of the three studies, INTRON A therapy resulted in a



282 reduction in serum alanine aminotransferase (ALT) in a greater proportion of
283 patients vs. control patients at the end of 6 months of dosing. During the 6 months
284 of follow-up, approximately 50% of the patients who responded maintained their ALT
285 response. A combined analysis comparing pretreatment and posttreatment liver
286 biopsies revealed histological improvement in a statistically significantly greater
287 proportion of INTRON A treated patients compared to controls.

288 Two additional studies have investigated longer treatment durations (up to
289 24 months).^{5,6} Patients in the two studies to evaluate longer duration of treatment
290 had hepatitis with or without cirrhosis in the absence of decompensated liver
291 disease. Complete response to treatment was defined as normalization of the final
292 two serum ALT levels during the treatment period. A sustained response was
293 defined as a complete response at the end of the treatment period with sustained
294 normal ALT values lasting at least 6 months following discontinuation of therapy.

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

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

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

318 Combination treatment with INTRON A and REBETOL[®] (ribavirin, USP)
319 provided a significant reduction in virologic load and improved histologic response in
320 adult patients with compensated liver disease who were treatment naïve or had
321 relapsed following therapy with alfa interferon alone; pediatric patients previously
322 untreated with alfa interferon experienced a sustained virologic response. See
323 REBETOL package insert for additional information.

324
325 **Chronic Hepatitis B Adults** The safety and efficacy of INTRON A in the treatment
326 of chronic hepatitis B were evaluated in three clinical trials in which INTRON A
327 doses of 30 to 35 million IU per week were administered subcutaneously (SC), as

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

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

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

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

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

358 In an ongoing study to assess the long-term durability of virologic response,
359 64 patients responding to INTRON A therapy have been followed for 1.1 to 6.6 years
360 after treatment; 95% (61/64) remain serum HBeAg negative and 49% (30/61) lost
361 serum HBsAg.

362 INTRON A therapy resulted in normalization of serum ALT in a significantly
363 greater proportion of treated patients compared to untreated patients in each of two
364 controlled studies (see TABLE 4). In a third study without a concurrent control
365 group, normalization of serum ALT was observed in 50% (12/24) of patients
366 receiving INTRON A therapy.

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

371 Improvement in liver histology was evaluated in Studies 1 and 3 by
372 comparison of pretreatment and 6 month posttreatment liver biopsies using the
373 semiquantitative Knodell Histology Activity Index.⁹ No statistically significant

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

385
 386 **Pediatrics** The safety and efficacy of INTRON A in the treatment of chronic
 387 hepatitis B was evaluated in one randomized controlled trial of 149 patients ranging
 388 from 1 year to 17 years of age. Seventy-two patients were treated with 3 million
 389 IU/m² of INTRON A therapy administered subcutaneously three times a week (TIW)
 390 for 1 week; the dose was then escalated to 6 million IU/m² TIW for a minimum of 16
 391 weeks up to 24 weeks. The maximum weekly dosage was 10 million IU TIW.
 392 Seventy-seven patients were untreated controls. Study entry and response criteria
 393 were identical to those described in the adult patient population.

394 Patients treated with INTRON A therapy had a better response (loss of HBV
 395 DNA and HBeAg at 24 weeks of follow-up) compared to the untreated controls (24%
 396 [17/72] vs. 10% [8/77] $p=0.05$). Sixteen of the 17 responders treated with INTRON A
 397 therapy remained HBV DNA and HBeAg negative and had a normal serum ALT 12
 398 to 24 months after completion of treatment. Serum HBsAg became negative in 7 out
 399 of 17 patients who responded to INTRON A therapy. None of the control patients
 400 who had an HBV DNA and HBeAg response became HBsAg negative. At 24 weeks
 401 of follow-up, normalization of serum ALT was similar in patients treated with
 402 INTRON A therapy (17%, 12/72) and in untreated control patients (16%, 12/77).
 403 Patients with a baseline HBV DNA <100 pg/mL were more likely to respond to
 404 INTRON A therapy than were patients with a baseline HBV DNA >100 pg/mL (35%
 405 vs. 9%, respectively). Patients who contracted hepatitis B through maternal vertical
 406 transmission had lower response rates than those who contracted the disease by
 407 other means (5% vs. 31%, respectively). There was no evidence that the effects on
 408 HBV DNA and HBeAg were limited to specific subpopulations based on age, gender,
 409 or race.

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 411

TABLE 1
 RESPONSE BY BASELINE CD4 COUNT^a 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%)
			} 58%	
CD4>400	5/7	(71%)	0/0	(0%)

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



412

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.

413

414

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		
1 ⁷	15/38 (39%)	--	--	3/42 (7%)	0.0009
2	--	--	10/24 (42%)	1/22 (5%)	0.005
3 ⁸	--	--	13/24 [§] (54%)	2/27 (7%) [§]	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).

415

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		
1	16/38 (42%)	--	--	8/42 (19%)	0.03
2	--	--	10/24 (42%)	1/22 (5%)	0.0034
3	--	--	12/24 [‡] (50%)	2/27 (7%) [‡]	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).

416

417

INDICATIONS AND USAGE



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

420

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

424

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

430

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

435

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

436

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

442

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

449

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

457

- 457 • No history of hepatic encephalopathy, variceal bleeding, ascites, or other
458 clinical signs of decompensation
- 459 • Bilirubin ≤ 2 mg/dL
- 460 • Albumin Stable and within normal limits
- 461 • Prothrombin Time < 3 seconds prolonged



- 462 • WBC $\geq 3000/\text{mm}^3$
 463 • Platelets $\geq 70,000/\text{mm}^3$

464

465 Serum creatinine should be normal or near normal.

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

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

476 INTRON A in combination with REBETOL is indicated for the treatment of
 477 chronic hepatitis C in patients 3 years of age and older with compensated liver
 478 disease previously untreated with alfa interferon therapy and in patients 18 years of
 479 age and older who have relapsed following alfa interferon therapy. See REBETOL
 480 package insert for additional information.

481

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

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

496

497 • No history of hepatic encephalopathy, variceal bleeding, ascites, or other
 498 signs of clinical decompensation

499 • Bilirubin Normal

500 • Albumin Stable and within normal limits

501 • Prothrombin Time *Adults* <3 seconds prolonged

502 *Pediatrics* ≤ 2 seconds prolonged

503 • WBC $\geq 4000/\text{mm}^3$



- 504 • Platelets *Adults* $\geq 100,000/\text{mm}^3$
 505 *Pediatrics* $\geq 150,000/\text{mm}^3$
 506

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

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

531 **CONTRAINDICATIONS**

532 INTRON A is contraindicated in patients with:

- 533 • Hypersensitivity to interferon alfa or any component of the product.
- 534 • Autoimmune hepatitis
- 535 • Decompensated liver disease

536
 537 **INTRON A and REBETOL combination therapy is additionally**
 538 contraindicated in:

- 539 • Patients with hypersensitivity to ribavirin or any other component of the
 540 product
- 541 • Women who are pregnant
- 542 • Men whose female partners are pregnant
- 543 • Patients with hemoglobinopathies (e.g. thalassemia major, sickle cell anemia)
- 544 • **Patients with creatinine clearance < 50 mL/min**

545 See REBETOL package insert for additional information.
 546

547 **WARNINGS**

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

556

557 **Cardiovascular Disorders**

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

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

574

575 **Cerebrovascular Disorders**

576

577 Ischemic and hemorrhagic cerebrovascular events have been observed in patients
578 treated with interferon alfa-based therapies, including INTRON A. Events occurred in
579 patients with few or no reported risk factors for stroke, including patients less than 45
580 years of age. Because these are spontaneous reports, estimates of frequency
581 cannot be made and a causal relationship between interferon alfa-based therapies
582 and these events is difficult to establish.

583

584 **Neuropsychiatric Disorders**

585 DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL
586 IDEATION, SUICIDAL ATTEMPTS, AND COMPLETED SUICIDES, AND
587 AGGRESSIVE BEHAVIOR, SOMETIMES DIRECTED TOWARDS OTHERS, HAVE
588 BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALFA
589 INTERFERONS, INCLUDING INTRON A THERAPY. If patients develop psychiatric
590 problems, including clinical depression, it is recommended that the patients be
591 carefully monitored during treatment and in the 6-month follow-up period.

592 Patients with a preexisting psychiatric condition, especially depression, or a history
593 of severe psychiatric disorder should not be treated with INTRON A.¹¹ INTRON A



594 therapy should be discontinued for any patient developing severe depression or
595 other psychiatric disorder during treatment. Obtundation and coma have also been
596 observed in some patients, usually elderly, treated at higher doses. While these
597 effects are usually rapidly reversible upon discontinuation of therapy, full resolution
598 of symptoms has taken up to 3 weeks in a few severe episodes. **If psychiatric**
599 **symptoms persist or worsen, or suicidal ideation or aggressive behavior towards**
600 **others is identified, it is recommended that treatment with INTRON A be**
601 **discontinued and the patient followed, with psychiatric intervention as appropriate.**
602 Narcotics, hypnotics, or sedatives may be used concurrently with caution and
603 patients should be closely monitored until the adverse effects have resolved.
604 Suicidal ideation or attempts occurred more frequently among pediatric patients,
605 primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment
606 and off therapy follow up. **Cases of encephalopathy have also been observed in**
607 **some patients, usually elderly, treated with higher doses of INTRON A.**
608
609

610 **Bone marrow toxicity**

611 INTRON A therapy suppresses bone marrow function and may result in
612 severe cytopenias including aplastic anemia. It is advised that complete blood
613 counts (CBC) be obtained pretreatment and monitored routinely during therapy (see
614 **PRECAUTIONS: Laboratory Tests**). INTRON A therapy should be discontinued in
615 patients who develop severe decreases in neutrophil ($<0.5 \times 10^9/L$) or platelet counts
616 ($<25 \times 10^9/L$) (see **DOSAGE AND ADMINISTRATION: Guidelines for Dose**
617 **Modification**).
618

619 **Ophthalmologic Disorders**

620 Decrease or loss of vision, retinopathy including macular edema, retinal artery
621 or vein thrombosis, retinal hemorrhages and cotton wool spots; optic neuritis and
622 papilledema may be induced or aggravated by treatment with Interferon alfa-2b or
623 other alpha interferons. All patients should receive an eye examination at baseline.
624 Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive
625 retinopathy) should receive periodic ophthalmologic exams during interferon alpha
626 treatment. Any patient who develops ocular symptoms should receive a prompt and
627 complete eye examination. Interferon alfa-2b treatment should be discontinued in
628 patients who develop new or worsening ophthalmologic disorders.
629

630 **Endocrine Disorders**

631 Infrequently, patients receiving INTRON A therapy developed thyroid
632 abnormalities, either hypothyroid or hyperthyroid. The mechanism by which
633 INTRON A may alter thyroid status is unknown. Patients with preexisting thyroid
634 abnormalities whose thyroid function cannot be maintained in the normal range by
635 medication should not be treated with INTRON A. Prior to initiation of INTRON A
636 therapy, serum TSH should be evaluated. Patients developing symptoms consistent
637 with possible thyroid dysfunction during the course of INTRON A therapy should
638 have their thyroid function evaluated and appropriate treatment instituted. Therapy
639 should be discontinued for patients developing thyroid abnormalities during



640 treatment whose thyroid function cannot be normalized by medication.
641 Discontinuation of INTRON A therapy has not always reversed thyroid dysfunction
642 occurring during treatment. Diabetes mellitus has been observed in patients treated
643 with alpha interferons. Patients with these conditions who cannot be effectively
644 treated by medication should not begin INTRON A therapy. Patients who develop
645 these conditions during treatment and cannot be controlled with medication should
646 not continue INTRON A therapy.

647

648 **Gastrointestinal Disorders**

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

653

654 **Pulmonary Disorders**

655 Pulmonary infiltrates, pneumonitis and pneumonia, including fatality, have
656 been observed in interferon alfa treated patients, including those treated with
657 INTRON A. The etiologic explanation for these pulmonary findings has yet to be
658 established. Any patient developing fever, cough, dyspnea, or other respiratory
659 symptoms should have a chest x-ray taken. If the chest X-ray shows pulmonary
660 infiltrates or there is evidence of pulmonary function impairment, the patient should
661 be closely monitored and, if appropriate, interferon alfa treatment should be
662 discontinued. While this has been reported more often in patients with chronic
663 hepatitis C treated with interferon alfa, it has also been reported in patients with
664 oncologic diseases treated with interferon alfa.

665

666 **Autoimmune Disorders**

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

675

676 **Human Albumin**

677 The powder formulations of this product contain albumin, a derivative of
678 human blood. Based on effective donor screening and product manufacturing
679 processes, it carries an extremely remote risk for transmission of viral diseases. A
680 theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is
681 considered extremely remote. No cases of transmission of viral diseases or CJD
682 have ever been identified for albumin.

683

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



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

693

694 **Chronic Hepatitis C and Chronic Hepatitis B** Patients with decompensated liver
695 disease, autoimmune hepatitis or a history of autoimmune disease, and patients who
696 are immunosuppressed transplant recipients should not be treated with INTRON A.
697 There are reports of worsening liver disease, including jaundice, hepatic
698 encephalopathy, hepatic failure, and death following INTRON A therapy in such
699 patients. Therapy should be discontinued for any patient developing signs and
700 symptoms of liver failure.

701 Chronic hepatitis B patients with evidence of decreasing hepatic synthetic
702 functions, such as decreasing albumin levels or prolongation of prothrombin time,
703 who nevertheless meet the entry criteria to start therapy, may be at increased risk of
704 clinical decompensation if a flare of aminotransferases occurs during INTRON A
705 treatment. In such patients, if increases in ALT occur during INTRON A therapy for
706 chronic hepatitis B, they should be followed carefully including close monitoring of
707 clinical symptomatology and liver function tests, including ALT, prothrombin time,
708 alkaline phosphatase, albumin, and bilirubin. In considering these patients for
709 INTRON A therapy, the potential risks must be evaluated against the potential
710 benefits of treatment.

711

712 **Use with Ribavirin (See also REBETOL Package Insert)** REBETOL may cause
713 birth defects and/or death of the unborn child. REBETOL therapy should not be
714 started until a report of a negative pregnancy test has been obtained immediately
715 prior to planned initiation of therapy. Patients should use at least two forms of
716 contraception and have monthly pregnancy tests (See **CONTRAINDICATIONS** and
717 **PRECAUTIONS**: Information for Patients).

718

719 Combination treatment with INTRON A and REBETOL was associated with
720 hemolytic anemia. Hemoglobin <10 g/dL was observed in approximately 10% of
721 adult and pediatric patients in clinical trials. Anemia occurred within 1 to 2 weeks of
722 initiation of ribavirin therapy. Combination treatment with INTRON A and REBETOL
723 should **not** be used in patients with creatinine clearance <50 mL/min. See
724 REBETOL package insert for additional information.

725

726 **PRECAUTIONS**

727 **General** Acute serious hypersensitivity reactions (e.g., urticaria, angioedema,
728 bronchoconstriction, anaphylaxis) have been observed rarely in INTRON A treated
729 patients; if such an acute reaction develops, the drug should be discontinued
730 immediately and appropriate medical therapy instituted. Transient rashes have



731 occurred in some patients following injection, but have not necessitated treatment
732 interruption.

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

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

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

742

743 **Triglycerides** Elevated triglyceride levels have been observed in patients treated
744 with interferons including INTRON A therapy. Elevated triglyceride levels should be
745 managed as clinically appropriate. Hypertriglyceridemia may result in pancreatitis.
746 Discontinuation of INTRON A therapy should be considered for patients with
747 persistently elevated triglycerides (e.g., triglycerides >1000 mg/dL) associated with
748 symptoms of potential pancreatitis, such as abdominal pain, nausea, or vomiting.

749

750 **Drug Interactions** Interactions between INTRON A and other drugs have not been
751 fully evaluated. Caution should be exercised when administering INTRON A therapy
752 in combination with other potentially myelosuppressive agents such as zidovudine.
753 Concomitant use of alfa interferon and theophylline decreases theophylline
754 clearance, resulting in a 100% increase in serum theophylline levels.

755

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

761

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

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

776

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

781

782 **Dental and Periodontal Disorders** Dental and periodontal disorders have been
783 reported in patients receiving ribavirin and interferon combination therapy. In
784 addition, dry mouth could have a damaging effect on teeth and mucous membranes
785 of the mouth during long-term treatment with the combination of REBETOL and
786 interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have
787 regular dental examinations. In addition some patients may experience vomiting. If
788 this reaction occurs, they should be advised to rinse out their mouth thoroughly
789 afterwards.

790

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

794

- 795 • Standard hematologic tests - including hemoglobin, complete and
796 differential white blood cell counts, and platelet count
- 797 • Blood chemistries - electrolytes, liver function tests, and TSH

798

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

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

806 Baseline chest X-rays are suggested and should be repeated if clinically
807 indicated.

808 For malignant melanoma patients, differential WBC count and liver function
809 tests should be monitored weekly during the induction phase of therapy and monthly
810 during the maintenance phase of therapy.

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

813

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

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

822

Mutagenicity studies have demonstrated that INTRON A is not mutagenic.

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

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

831 INTRON A in combination with REBETOL should be used with caution in
832 fertile men. See REBETOL package insert for additional information.

833

834 **Pregnancy Category C** INTRON A has been shown to have abortifacient effects in
835 *Macaca mulatta* (rhesus monkeys) at 15 and 30 million IU/kg (estimated human
836 equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a
837 60-kg adult). There are no adequate and well-controlled studies in pregnant women.
838 INTRON A therapy should be used during pregnancy only if the potential benefit
839 justifies the potential risk to the fetus.

840

841 **Pregnancy Category X** applies to combination treatment with INTRON A and
842 REBETOL (see **CONTRAINDICATIONS**). See REBETOL package insert for
843 additional information. Significant teratogenic and/or embryocidal effects have been
844 demonstrated in all animals species exposed to ribavirin. REBETOL therapy is
845 contraindicated in women who are pregnant and in the male partners of women who
846 are pregnant. See **CONTRAINDICATIONS** and the REBETOL package insert.

847 **Ribavirin Pregnancy Registry: A Ribavirin Pregnancy Registry has been**
848 **established to monitor maternal-fetal outcomes of pregnancies in female**
849 **patients and female partners of male patients exposed to ribavirin during**
850 **treatment and for 6 months following cessation of treatment. Physicians and**
851 **patients are encouraged to report such cases by calling 1-800-593-2214.**

852

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

858

859 **Pediatric Use** *General Safety* and effectiveness in pediatric patients have not been
860 established for indications other than chronic hepatitis B and chronic hepatitis C.

861 *Chronic Hepatitis B* Safety and effectiveness in pediatric patients ranging in age
862 from 1 to 17 years have been established based upon one controlled clinical trial
863 (see **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, DOSAGE AND**
864 **ADMINISTRATION; Chronic Hepatitis B**).

865

866 *Chronic Hepatitis C*

867 Safety and effectiveness in pediatric patients ranging in age from 3 to 16 years have
868 been established based upon clinical studies in 118 patients. See REBETOL

869 package insert for additional information. Suicidal ideation or attempts occurred
870 more frequently among pediatric patients compared to adult patients (2.4% versus
871 1 %) during treatment and off-therapy follow-up (See **WARNINGS,**
872 **Neuropsychiatric Disorders**). During a 48-week course of therapy there was a
873 decrease in the rate of linear growth (mean percentile assignment decrease of 7%)
874 and a decrease in the rate of weight gain (mean percentile assignment decrease of
875 9%). A general reversal of these trends was noted during the 24-week post-
876 treatment period.

877

878 **Geriatric Use** In all clinical studies of INTRON A (Interferon alfa-2b, recombinant),
879 including studies as monotherapy and in combination with REBETOL (ribavirin,
880 USP) Capsules, only a small percentage of the subjects were aged 65 and over.
881 These numbers were too few to determine if they respond differently from younger
882 subjects except for the clinical trials of INTRON A in combination with REBETOL,
883 where elderly subjects had a higher frequency of anemia (67%) than did younger
884 patients.(28%).

885 In a database consisting of clinical study and postmarketing reports for
886 various indications, cardiovascular adverse events and confusion were reported
887 more frequently in elderly patients receiving INTRON A therapy compared to
888 younger patients.

889 In general, INTRON A therapy should be administered to elderly patients
890 cautiously, reflecting the greater frequency of decreased hepatic, renal, bone
891 marrow, and/or cardiac function and concomitant disease or other drug therapy.
892 INTRON A is known to be substantially excreted by the kidney, and the risk of
893 adverse reactions to INTRON A may be greater in patients with impaired renal
894 function. Because elderly patients often have decreased renal function, patients
895 should be carefully monitored during treatment, and dose adjustments made based
896 on symptoms and/or laboratory abnormalities (see **CLINICAL PHARMACOLOGY,**
897 and **DOSAGE AND ADMINISTRATION**).

898

899 **ADVERSE REACTIONS**

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

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

907

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 ¹	CHRONIC HEPATITIS B		
							Adults	Pediatrics		
	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/S C	35 MIU QD/S C	3 MIU TIW	5 MIU QD	10 MIU TIW	6 MIU/m ² TIW
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
<u>Application-Site Disorders</u>			20							
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									
<u>Blood Disorders (<5%)</u>	anemia, anemia hypochromic, granulocytopenia, hemolytic anemia, leukopenia, lymphocytosis, neutropenia (9% in chronic hepatitis C, 14% in chronic hepatitis B pediatrics), thrombocytopenia (10% in chronic hepatitis C) (bleeding 8% in malignant melanoma), thrombocytopenia purpura									
<u>Body as a Whole</u>										
facial edema	--	1	--	<1	--	10	<1	3	1	<1
weight decrease	3	13	<1	<1	5	3	10	2	5	3
other (≤5%)	allergic reaction, cachexia, dehydration, earache, hernia, edema, hypercalcemia, hyperglycemia, hypothermia, inflammation nonspecific, lymphadenitis, lymphadenopathy, mastitis, periorbital edema, poor peripheral circulation, peripheral edema (6% in follicular lymphoma), phlebitis superficial, scrotal/penile edema, thirst, weakness, weight increase									
<u>Cardiovascular System Disorders (<5%)</u>	angina, arrhythmia, atrial fibrillation, bradycardia, cardiac failure, cardiomegaly, cardiomyopathy, coronary artery disorder, extrasystoles, heart valve disorder, hematoma, hypertension (9% in chronic hepatitis C), hypotension, palpitations, phlebitis, postural hypotension, pulmonary embolism, Raynaud's disease, tachycardia, thrombosis, varicose vein									
<u>Endocrine System Disorders (<5%)</u>	aggravation of diabetes mellitus, goiter, gynecomastia, hyperglycemia, hyperthyroidism, hypertriglyceridemia, hypothyroidism, virilism									
<u>Flu-like Symptoms</u>										
fever	81	56	68	56	47	55	34	66	86	94
headache	62	21	39	47	36	21	43	61	44	57
chills	54	--	46	45	--	--	--	--	--	--
myalgia	75	16	39	44	34	28	43	59	40	27
fatigue	96	8	61	18	84	48	23	75	69	71
increased sweating	6	13	8	2	4	21	4	1	1	3
asthenia	--	63	7	--	11	--	40	5	15	5
rigors	2	7	--	--	30	14	16	38	42	30
arthralgia	6	8	8	9	--	3	16	19	8	15
dizziness	23	--	12	9	7	24	9	13	10	8
influenza-like symptoms	10	18	37	--	45	79	26	5	--	<1
back pain	--	15	19	6	1	3	--	--	--	--
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									
<u>Gastrointestinal System Disorders</u>										
diarrhea	35	19	18	2	18	45	13	19	8	12
anorexia	69	21	19	1	38	41	14	43	53	43



Treatment-Related Adverse Experiences By Indication

ADVERSE EXPERIENCE	Dosing Regimens Percentage (%) of Patients									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSII'S SARCOMA		CHRONIC HEPATITIS C ^{II}	CHRONIC HEPATITIS B		
								Adults	Pediatrics	
	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/S C	35 MIU QD/S C	3 MIU TIW	5 MIU QD	10 MIU TIW	6 MIU/m ² TIW
	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
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	†	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%)	arteritis, arthritis, arthritis aggravated, arthrosis, bone disorder, bone pain, carpal tunnel syndrome, hyporeflexia, leg cramps, muscle atrophy, muscle weakness, polyarteritis nodosa, tendinitis, rheumatoid arthritis, spondylitis									
Nervous System and Psychiatric Disorders										
depression	40	9	6	3	9	28	19	17	6	4
paresthesia	13	13	6	1	3	21	5	6	3	<1
impaired concentration	--	1	--	<1	3	14	3	8	5	3
amnesia	§	1	<5	--	--	14	--	--	--	--
confusion	8	2	<5	4	12	10	1	--	--	2
hypoesthesia	--	1	<5	1	--	10	--	--	--	--
irritability	1	1	--	--	--	--	13	16	12	22
somnolence	1	2	<5	3	3	--	33 [¶]	14	9	5
anxiety	1	9	5	<1	1	3	5	2	--	3
insomnia	5	4	--	<1	3	3	12	11	6	8
nervousness	1	1	--	1	--	3	2	3	--	3
decreased libido	1	1	<5	--	--	--	1	5	1	--
other (<5%)	abnormal coordination, abnormal dreaming, abnormal gait, abnormal thinking, aggravated depression, aggressive reaction, agitation (7% in chronic hepatitis B pediatrics), alcohol intolerance, apathy, aphasia, ataxia, Bell's palsy, CNS dysfunction, coma, convulsions, delirium, dysphonia, emotional lability, extrapyramidal disorder, feeling of ebriety, flushing, hearing disorder, hearing impairment, hot flashes, hyperesthesia, hyperkinesia, hypertonia, hypokinesia, impaired consciousness, labyrinthine disorder, loss of consciousness, manic depression, manic reaction, migraine, neuralgia, neuritis, neuropathy, neurosis, paresis, paroniria, parosmia, personality disorder, polyneuropathy, psychosis, speech disorder, stroke, suicidal ideation, suicide attempt, syncope, tinnitus, tremor, twitching, vertigo (8% in follicular lymphoma)									
Reproduction System	amenorrhea (12% in follicular lymphoma), dysmenorrhea, impotence, leukorrhea, menorrhagia, menstrual irregularity, pelvic pain, penis disorder, sexual dysfunction, uterine bleeding, vaginal dryness									



Treatment-Related Adverse Experiences By Indication

ADVERSE EXPERIENCE	Dosing Regimens Percentage (%) of Patients									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOS'S SARCOMA		CHRONIC HEPATITIS C [†]	CHRONIC HEPATITIS B		
								Adults	Pediatrics	
	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/S C	35 MIU QD/S C	3 MIU TIW	5 MIU QD	10 MIU TIW	6 MIU/m ² TIW
	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
Disorders (<5%)										
Resistance Mechanism Disorders										
moniliasis	--	1	--	<1	--	17	--	--	--	--
herpes simplex	1	2	--	1	--	3	1	5	--	--
other (<5%)	abscess, conjunctivitis, fungal infection, hemophilus, herpes zoster, infection, infection bacterial, infection nonspecific (7% follicular lymphoma), infection parasitic, otitis media, sepsis, stye, trichomonas, upper respiratory tract infection, viral infection (7% in chronic hepatitis C)									
Respiratory System Disorders										
dyspnea	15	14	<1	--	1	34	3	5	--	--
coughing	6	13	<1	--	--	31	1	4	--	5
pharyngitis	2	8	<5	1	1	31	3	7	1	7
sinusitis	1	4	--	--	--	21	2	--	--	--
nonproductive coughing	2	7	--	--	--	14	0	1	--	--
nasal congestion	1	7	--	1	--	10	<1	4	--	--
other (≤5%)	asthma, bronchitis (10% in follicular lymphoma), bronchospasm, cyanosis, epistaxis (7% in chronic hepatitis B pediatrics), hemoptysis, hypoventilation, laryngitis, lung fibrosis, pleural effusion, orthopnea, pleural pain, pneumonia, pneumonitis, pneumothorax, rales, respiratory disorder, respiratory insufficiency, sneezing, tonsillitis, tracheitis, wheezing									
Skin and Appendages Disorders										
dermatitis	1	--	8	--	--	--	2	1	--	--
alopecia	29	23	8	--	12	31	28	26	38	17
pruritus	--	10	11	1	7	--	9	6	4	3
rash	19	13	25	--	9	10	5	8	1	5
dry skin	1	3	9	--	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, nonherpetic 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									
Urinary System Disorders (<5%)	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)									
Vision Disorders (<5%)	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



908 **Hairy Cell Leukemia** The adverse reactions most frequently reported during clinical
 909 trials in 145 patients with hairy cell leukemia were the "flu-like" symptoms of fever
 910 (68%), fatigue (61%), and chills (46%).

911

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

921 Adverse reactions classified as severe or life-threatening (ECOG Toxicity
 922 Criteria grade 3 or 4) were recorded in 66% and 14% of INTRON A treated patients,
 923 respectively. Severe adverse reactions recorded in >10% of INTRON A treated
 924 patients included neutropenia/leukopenia (26%), fatigue (23%), fever (18%), myalgia
 925 (17%), headache (17%), chills (16%), and increased SGOT (14%). Grade 4 fatigue
 926 was recorded in 4% and grade 4 depression was recorded in 2% of INTRON A
 927 treated patients. No other grade 4 AE was reported in more than 2 INTRON A
 928 treated patients. Lethal hepatotoxicity occurred in 2 INTRON A treated patients
 929 early in the clinical trial. No subsequent lethal hepatotoxicities were observed with
 930 adequate monitoring of liver function tests (see **PRECAUTIONS - Laboratory**
 931 **Tests**).

932

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

944 Twenty-eight percent of CHVP plus INTRON A treated patients had a
 945 temporary modification/interruption of their INTRON A therapy, but only 13 patients
 946 (10%) permanently stopped INTRON A therapy because of toxicity. There were
 947 4 deaths on study; two patients committed suicide in the CHVP plus INTRON A arm
 948 and two patients in the CHVP arm had unwitnessed sudden death. Three patients
 949 with hepatitis B (one of whom also had alcoholic cirrhosis) developed hepatotoxicity
 950 leading to discontinuation of INTRON A. Other reasons for discontinuation included
 951 intolerable asthenia (5/135), severe flu symptoms (2/135), and one patient each with
 952 exacerbation of ankylosing spondylitis, psychosis, and decreased ejection fraction.

953

954 **Condylomata Acuminata** Eighty-eight percent (311/352) of patients treated with
 955 INTRON A for condylomata acuminata who were evaluable for safety, reported an
 956 adverse reaction during treatment. The incidence of the adverse reactions reported
 957 increased when the number of treated lesions increased from one to five. All 40
 958 patients who had five warts treated, reported some type of adverse reaction during
 959 treatment.

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

963

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

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

980

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

990 Of the patients achieving a complete response after 6 months of therapy,
 991 12/79 (15%) subsequently discontinued INTRON A treatment during extended
 992 therapy because of adverse events, and 23/79 (29%) experienced severe adverse
 993 events (WHO grade 3 or 4) during extended therapy.

994 In patients using combination treatment with INTRON A and REBETOL, the
 995 primary toxicity observed was hemolytic anemia. Reductions in hemoglobin levels
 996 occurred within the first 1 to 2 weeks of therapy. Cardiac and pulmonary events
 997 associated with anemia occurred in approximately 10% of patients treated with
 998 INTRON A/REBETOL therapy. See REBETOL package insert for additional
 999 information.



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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												
	HAIRY CELL LEUKEMIA			CONDYLOMATA ACUMINATA			AIDS-RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C		CHRONIC HEPATITIS B		Pediatrics
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	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	3 MIU TIW	5 MIU QD	10 MIU TIW	6 MIU/m ² TIW	
Hemoglobin	22	8	N=135	N=145	N=352	N=69-73	N=26-28	N=140-171	N=96-101	N=75-103	N=113-115		
White Blood Cell Count	"	--		NA	--	1	15	26 [†]	32 [†]	23 [†]	17 [†]		
Platelet Count	15	--		NA	17	10	22	26 [†]	68 [†]	34 [†]	9 [†]		
Serum Creatinine	3	2		0	--	0	8	15 [‡]	12 [‡]	5 [‡]	1 [‡]		
Alkaline Phosphatase	13	--		4	--	--	--	6	3	0	3		
Lactate Dehydrogenase	1	--		0	--	--	--	--	8	4	0		
Serum Urea Nitrogen	12	4		0	--	--	--	--	--	--	--		
SGOT	63	24		4	12	11	41	--	2	0	2		
SGPT	2	--		13	--	10	15	--	--	--	--		
Granulocyte Count													
• Total	92	36		NA	--	31	39	45 [§]	75 [§]	61 [§]	70 [§]		
• 1000-<1500/mm ³	66	--		--	--	--	--	32	30	32	43		
• 750-<1000/mm ³	--	21		--	--	--	--	10	24	18	18		
• 500-<750/mm ³	25	--		--	--	--	--	1	17	9	7		
• <500/mm ³	1	13		--	--	--	--	2	4	2	2		

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/mm³
- ‡ Decrease to <70,000/mm³
- § 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



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1025 Postmarketing Experience

1026 The following adverse reactions have been identified during postapproval use of
1027 INTRON A: nephrotic syndrome, renal failure, renal insufficiency, pancreatitis,
1028 psychosis including hallucinations, Stevens Johnson syndrome, toxic epidermal
1029 necrolysis, erythema multiforme, injection site necrosis, myositis, and hearing loss.
1030 A wide variety of autoimmune and immune-mediated disorders have been reported
1031 with alpha interferons including idiopathic thrombocytopenic purpura and thrombotic
1032 thrombocytopenic purpura. Additionally, the following adverse reactions have been
1033 identified during postapproval use of INTRON A alone or in combination with
1034 REBETOL: aplastic anemia and pure red cell aplasia. Sarcoidosis or exacerbation of
1035 sarcoidosis has been reported. Because these reactions are reported voluntarily
1036 from a population of uncertain size, it is not always possible to reliably estimate their
1037 frequency or establish a causal relationship to drug exposure.

1038

1039 OVERDOSAGE

1040 There is limited experience with overdose. Postmarketing surveillance includes
1041 reports of patients receiving a single dose as great as 10 times the recommended
1042 dose. In general, the primary effects of an overdose are consistent with the effects
1043 seen with therapeutic doses of interferon alfa-2b. Hepatic enzyme abnormalities,
1044 renal failure, hemorrhage, and myocardial infarction have been reported with single
1045 administration overdoses and/or with longer durations of treatment than prescribed
1046 (see **ADVERSE REACTIONS**). Toxic effects after ingestion of interferon alfa-2b are
1047 not expected because interferons are poorly absorbed orally. Consultation with a
1048 poison center is recommended.

1049

1050 **Treatment.** There is no specific antidote for interferon alfa-2b. Hemodialysis and
1051 peritoneal dialysis are not considered effective for treatment of overdose.

1052

1053 DOSAGE AND ADMINISTRATION

1054

1055 General

1056

1057 **IMPORTANT: INTRON A** is supplied as 1) Powder for Injection/Reconstitution; 2)
1058 Solution for Injection in Vials; 3) Solution for Injection in Multidose Pens. **Not all**
1059 **dosage forms and strengths are appropriate for some indications.** It is
1060 important that you carefully read the instructions below for the indication you are
1061 treating to ensure you are using an appropriate dosage form and strength.

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1063 To enhance the tolerability of INTRON A, injections should be administered in the
1064 evening when possible.

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1066 To reduce the incidence of certain adverse reactions, acetaminophen may be
1067 administered at the time of injection.

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1069 **Hairy Cell Leukemia (see DOSAGE AND ADMINISTRATION, General)**

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1071 **Dose:** The recommended dose for the treatment of hairy cell leukemia is 2 million
1072 IU/m² administered intramuscularly or subcutaneously 3 times a week for up to 6
1073 months. Patients with platelet counts of less than 50,000/mm³ should not be
1074 administered INTRON A intramuscularly, but instead by subcutaneous
1075 administration. Patients who are responding to therapy may benefit from continued
1076 treatment.

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Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single-dose)	10 MIU/mL	IM, SC	N/A
Solution 10 MIU (single-dose)	10 MIU/mL	SC	N/A
Solution 18 MIU multidose	6 MIU/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

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

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Dose adjustment:

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- 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 months of treatment.

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Malignant Melanoma (see DOSAGE AND ADMINISTRATION, General)

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

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Induction Recommended Dose:

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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 Adjustment below).

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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

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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.

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

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Dose adjustment:

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1115 **NOTE:** Regular laboratory testing should be performed to monitor laboratory
 1116 abnormalities for the purpose of dose modifications (see **PRECAUTIONS-**
 1117 **Laboratory Tests**).

- 1118
- 1119 • INTRON A should be withheld for severe adverse reactions, including
 1120 granulocyte counts $>250\text{mm}^3$ but $<500\text{mm}^3$ or SGPT/SGOT $>5\text{-}10\text{x}$ upper
 1121 limit of normal, until adverse reactions abate. INTRON A treatment should be
 1122 restarted at 50% of the previous dose.
 - 1123 • INTRON A should be permanently discontinued for:
 1124 ○ Toxicity that does not abate after withholding INTRON A
 1125 ○ Severe adverse reactions which recur in patients receiving reduced
 1126 doses of INTRON A
 1127 ○ Granulocyte count $<250\text{mm}^3$ or SGPT/SGOT of $>10\text{x}$ upper limit of
 1128 normal

1129

1130 Maintenance Recommended Dose:

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1132 The recommended dose of INTRON A for maintenance is 10 million IU/m² as a
 1133 subcutaneous injection three times per week for 48 weeks (see Dose adjustment
 1134 below).

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Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single-dose)*	10 MIU/mL	SC	N/A
Powder 18 MIU (single-dose)**	18 MIU/mL	SC	N/A
Solution 10 MIU	10 MIU/mL	SC	N/A
Solution 18 MIU multidose	6 MIU/mL	SC	N/A
Solution 25 MIU multidose	10 MIU/mL	SC	N/A
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

1137

*Patients receiving 50% dose reduction only

1138

**Patients receiving full dose only

1139

1140 **NOTE: INTRON A Powder for Injection does not contain a preservative. The**
 1141 **vial must be discarded after reconstitution and withdrawal of a single dose.**

1142

1142 Dose adjustment:

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1144 **NOTE:** Regular laboratory testing should be performed to monitor laboratory
 1145 abnormalities for the purpose of dose modifications (see **PRECAUTIONS-**
 1146 **Laboratory Tests**).

1147

- 1148 • INTRON A should be withheld for severe adverse reactions, including
 1149 granulocyte counts $>250\text{mm}^3$ but $<500\text{mm}^3$ or SGPT/SGOT $>5\text{-}10\text{x}$ upper
 1150 limit of normal, until adverse reactions abate. INTRON A treatment should be
 1151 restarted at 50% of the previous dose.

1152

- 1153 • INTRON A should be permanently discontinued for:
- 1154 ○ Toxicity that does not abate after withholding INTRON A
- 1155 ○ Severe adverse reactions which recur in patients receiving reduced
- 1156 doses of INTRON A
- 1157 ○ Granulocyte count $<250\text{mm}^3$ or SGPT/SGOT of $>10\text{x}$ upper limit of
- 1158 normal

1159

1160 **Follicular Lymphoma (see DOSAGE and ADMINISTRATION, General)**

1161

1162 **Dose:** The recommended dose of INTRON A for the treatment of follicular

1163 lymphoma is 5 million IU subcutaneously three times per week for up to 18 months

1164 in conjunction with anthracycline-containing chemotherapy regimen and following

1165 completion of the chemotherapy regimen.

1166

1167

Dosage Forms for this Indication

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

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1169 **NOTE: INTRON A Powder for Injection does not contain a preservative. The**

1170 **vial must be discarded after reconstitution and withdrawal of a single dose.**

1171

1172 **Dose adjustment:**

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- 1174 • Doses of myelosuppressive drugs were reduced by 25% from a full-dose
- 1175 CHOP regimen, and cycle length increased by 33% (eg, from 21 to 28 days)
- 1176 when alfa interferon was added to the regimen.
- 1177 • Delay chemotherapy cycle if neutrophil count was $<1500/\text{mm}^3$ or platelet
- 1178 count was $<75,000/\text{mm}^3$.
- 1179 • INTRON A should be permanently discontinued if SGOT exceeds $>5\text{x}$ the
- 1180 upper limit of normal or serum creatinine $>2.0\text{ mg/dl}$ (see **WARNINGS**).
- 1181 • Administration of INTRON A therapy should be withheld for a neutrophil count
- 1182 $<1000/\text{mm}^3$, or a platelet count $<50,000/\text{mm}^3$.
- 1183 • INTRON A dose should be reduced by 50% (2.5 MIU TIW) for a neutrophil
- 1184 count $>1000/\text{mm}^3$, but $<1500/\text{mm}^3$. The INTRON A dose may be re-
- 1185 escalated to the starting dose (5 million IU TIW) after resolution of
- 1186 hematologic toxicity ($\text{ANC} >1500/\text{mm}^3$).
- 1187

1188 **Condylomata Acuminata (see DOSAGE and ADMINISTRATION, General)**

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1190 **Dose:** The recommended dose is 1.0 million IU per lesion in a maximum of 5 lesions

1191 in a single course. The lesions should be injected three times weekly on alternate

1192 days for 3 weeks. An additional course may be administered at 12-16 weeks.

1193

1194

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

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

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1199

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

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- the 18 million or 50 million IU Powder for Injection

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- the 18 million IU multidose INTRON A Solution for Injection

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- the Multidose Pens

1203

1204

Dose adjustment: None

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Technique for Injection:

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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.

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

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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).

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Dosage Forms for this Indication

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

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NOTE: INTRON A Solution for Injection either in vials or in Multidose Pens should NOT be used for AIDS-Related Kaposi's Sarcoma.

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

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Dose adjustment:

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- 1241
- INTRON A dose should be reduced by 50% or withheld for severe adverse reactions.
 - INTRON A may be resumed at a 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.

1242 **Chronic Hepatitis C (see DOSAGE and ADMINISTRATION, General)**

1243

1244 **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.

1253

1254 When INTRON A is administered in combination with REBETOL, patients with impaired renal function and/or those over the age of 50 should be carefully monitored with respect to the development of anemia. See REBETOL package insert for dosing when used in combination with REBETOL for adults and pediatric patients.

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1260

1261 **Dosage Forms for this Indication**

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

1262

1263

1264 **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.

1268

1269 **Chronic Hepatitis B Adults (see DOSAGE and ADMINISTRATION, General)**

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1271 **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.

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1275

1276 **Dosage Forms for this Indication**

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single-dose)	10 MIU/mL	IM, SC	N/A
Solution 10 MIU (single-dose)	10 MIU/mL	SC	N/A

Solution 25 MIU multidose	10 MIU/mL	IM, SC	N/A
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

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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	N/A
Solution 10 MIU (single-dose)	10 MIU/mL	SC	N/A
Solution 25 MIU multidose	10 MIU/mL	SC	N/A
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

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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:

INTRON A Dose	White Blood Cell Count	Granulocyte Count	Platelet Count
Reduce 50%	<1.5 x 10 ⁹ /L	<0.75 x 10 ⁹ /L	<50 x 10 ⁹ /L
Permanently Discontinue	<1.0 x 10 ⁹ /L	<0.5 x 10 ⁹ /L	<25 x 10 ⁹ /L

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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 NOT RE-ENTER VIAL AFTER**

1313 **WITHDRAWING THE DOSE. DISCARD UNUSED PORTION** (see **DOSAGE and**
1314 **ADMINISTRATION**). Once the dose from the single-dose vial has been withdrawn,
1315 the sterility of any remaining product can no longer be guaranteed. Pooling of
1316 unused portions of some medications has been linked to bacterial contamination and
1317 morbidity.

1318

1319 • **Intramuscular, Subcutaneous, or Intralesional Administration**

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1321 Inject 1ml Diluent (Sterile Water for Injection, USP) for INTRON A into the INTRON
1322 A vial. Swirl gently to hasten complete dissolution of the powder. The appropriate
1323 INTRON A dose should then be withdrawn and injected intramuscularly,
1324 subcutaneously, or intralesionally (see **MEDICATION GUIDE** for detailed
1325 instructions).

1326

1327 Please refer to the **Medication Guide** for detailed, step-by-step instructions on how
1328 to inject the INTRON A dose. After preparation and administration of the INTRON A
1329 injection, it is essential to follow the procedure for proper disposal of syringes and
1330 needles (see **MEDICATION GUIDE** for detailed instructions).

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1332 Parenteral drug products should be inspected visually for particulate matter and
1333 discoloration prior to administration.

1334

1335 • **Intravenous Infusion**

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1337 The infusion solution should be prepared immediately prior to use. Based on the
1338 desired dose, the appropriate vial strength(s) of INTRON A should be reconstituted
1339 with the diluent provided. Inject 1 mL Diluent (Sterile Water for Injection, USP) for
1340 INTRON A into the INTRON A vial. Swirl gently to hasten complete dissolution of
1341 the powder. The appropriate INTRON A dose should then be withdrawn and
1342 injected into a 100-mL bag of 0.9% Sodium Chloride Injection, USP. The final
1343 concentration of INTRON A should not be less than 10 million IU/100mL.

1344

1345 Please refer to the **Medication Guide** for detailed, step-by-step instructions on how
1346 to inject the INTRON A dose. After preparation and administration of INTRON A, it
1347 is essential to follow the procedure for proper disposal of syringes and needles.

1348

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1350 **INTRON A Solution for Injection in Vials**

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1352 INTRON A Solution for Injection is supplied in a single-use vial and two multidose
1353 vials. The solutions for injection do not require reconstitution prior to administration;
1354 the solution is clear and colorless.

1355

1356 The appropriate dose should be withdrawn from the vial and injected
1357 intramuscularly, subcutaneously, or intralesionally.

1358

1359 The single-use 10 million IU vial is supplied with B-D Safety-Lok* syringes. The
 1360 Safety-Lok* syringe contains a plastic safety sleeve to be pulled over the needle
 1361 after use. The syringe locks with an audible click when the green stripe on the
 1362 safety sleeve covers the red stripe on the needle. The B-D Safety-Lok* syringes
 1363 provided with the 10 MIU Solution for Injection cannot be used for IM injections.

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 1365 **INTRON A Solution for Injection is not recommended for intravenous**
 1366 **administration.**

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 1368 **Solution for Injection in Multidose Pens**

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 1370 The INTRON A Solution for Injection Multidose Pens are designed to deliver 3-12
 1371 doses depending on the individual dose using a simple dial mechanism and are for
 1372 subcutaneous injections only. Only the needles provided in the packaging should be
 1373 used for the INTRON A Solution for Injection Multidose Pen. A new needle is to be
 1374 used each time a dose is delivered using the pen. To avoid the possible
 1375 transmission of disease, each INTRON A Solution for Injection Multidose Pen is for
 1376 single patient use only.

1377
 1378 Please refer to the **Medication Guide** for detailed, step-by-step instructions on how
 1379 to inject the INTRON A dose. After preparation and administration of INTRON A, it
 1380 is essential to follow the procedure for proper disposal of syringes and needles.

1381
 1382 **HOW SUPPLIED**

1383
 1384 **INTRON A Powder for Injection**

1385 INTRON A Powder for Injection, 10 million IU per vial and Diluent for INTRON
 1386 A (Sterile Water for Injection, USP) 1 mL per vial; boxes containing 1 INTRON A vial
 1387 and 1 vial of INTRON A Diluent (NDC 0085-0571-02).

1388 INTRON A Powder for Injection, 18 million IU per vial and Diluent for INTRON
 1389 A (Sterile Water for Injection, USP) 1 mL per vial; boxes containing 1 vial of
 1390 INTRON A and one vial of INTRON A Diluent (NDC 0085-1110-01).

1391 INTRON A Powder for Injection, 50 million IU per vial and Diluent for INTRON
 1392 A (Sterile Water for Injection, USP) 1 mL per vial; boxes containing 1 INTRON A vial
 1393 and 1 vial of INTRON A Diluent (NDC 0085-0539-01).

1394
 1395 **INTRON A Solution for Injection in Multidose Pens**

1396 INTRON A Solution for Injection, 6 doses of 3 million IU (18 million IU)
 1397 multidose pen (22.5 million IU per 1.5 mL per pen); boxes containing 1 INTRON A
 1398 multidose pen, six disposable needles and alcohol swabs (NDC 0085-1242-01).

1399 INTRON A Solution for Injection, 6 doses of 5 million IU (30 million IU)
 1400 multidose pen (37.5 million IU per 1.5 mL per pen); boxes containing 1 INTRON A
 1401 multidose pen, six disposable needles and alcohol swabs (NDC 0085-1235-01).

1402 INTRON A Solution for Injection, 6 doses of 10 million IU (60 million IU)
 1403 multidose pen (75 million IU per 1.5 mL per pen); boxes containing 1 INTRON A
 1404 multidose pen, six disposable needles and alcohol swabs (NDC 0085-1254-01).

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INTRON A Solution for Injection in Vials

INTRON A 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 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

Rev. 7/07

B-XXXXXXXXXT

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*Safety-Lok is a registered trademark of Becton Dickinson and Company.

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MEDICATION GUIDE

INTRON® A

(Interferon alfa-2b, recombinant)

Including appendix with instructions for using INTRON® A Powder for Injection

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

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

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

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

You should call your healthcare provider immediately if you develop any of these conditions while taking INTRON® A:

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

49 The most serious possible side effects of INTRON® A include:

50

51 **RISK TO PREGNANCY.** Combination INTRON® A and REBETOL® therapy can
52 cause death, serious birth defects or other harm to your unborn child. If you
53 are pregnant, you or your male partner must not take INTRON® A and
54 REBETOL® combination therapy. You must not become pregnant while either
55 you or your partner are taking the combination of INTRON® A and REBETOL®
56 and for 6 months after you stop taking the combination. If you are a woman of
57 childbearing age you must have negative pregnancy tests immediately before
58 starting treatment, during treatment and for 6 months after you have stopped
59 treatment. You should use two forms of birth control during and for 6 months
60 after you have stopped treatment. If you are a man taking INTRON®
61 A/REBETOL® combination therapy, one of the two forms of birth controls
62 should be a condom. You must use birth control even if you believe that you
63 are not fertile or that your fertility is low. You should talk to your healthcare
64 provider about birth control for you and your partner. If you or your partner
65 becomes pregnant while either of you is being treated or within 6 months of
66 stopping treatment tell your healthcare provider right away. There is a
67 Ribavirin Pregnancy Registry that collects information about pregnancy
68 outcomes in female patients and female partners of male patients exposed to
69 ribavirin. You or your healthcare provider are encouraged to contact the
70 Registry at 1-800-593-2214.

71

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

82

83 **Eye problems.** If you notice any changes in your eyesight such as difficulty seeing,
84 it could mean that your eyes are being affected, so you should call your healthcare
85 provider right away.

86

87 **Heart problems.** Some patients taking INTRON® A may develop problems with
88 their heart, including low blood pressure, fast heart rate, and very rarely, heart
89 attacks. Tell your healthcare provider if you have had any heart problems in the
90 past.

91

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

96

97 If you are taking INTRON® A and REBETOL® combination therapy, REBETOL®
98 can cause a drop in your number of red blood cells (anemia). A very low red blood
99 cell count can be dangerous especially if you have heart or breathing problems.
100 For other possible side effects of INTRON® A. see "*What are the possible side*
101 *effects of INTRON® A?*" in this Medication Guide.
102

103 **What is INTRON® A?**

104

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

108

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

112

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

115

116 **Who should not take INTRON® A?**

117

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

119

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

129

130 **If you have any of the following conditions or serious medical problems, tell**
131 **your healthcare provider before taking INTRON® A alone or in combination**
132 **with REBETOL®:**

133

- 134 • depression or anxiety
- 135 • eye problems
- 136 • sleep problems
- 137 • high blood pressure
- 138 • previous heart attack, or other heart problems
- 139 • liver problems (other than hepatitis B or C)
- 140 • any kind of autoimmune disease (where the body's immune system attacks the
141 body's own cells), such as psoriasis, sarcoidosis, systemic lupus erythematosus,
142 rheumatoid arthritis
- 143 • thyroid problems
- 144 • diabetes
- 145 • colitis (inflammation of the bowels)
- 146 • cancer
- 147 • hepatitis B or C infection
- 148 • HIV infection (the virus that causes AIDS)
- 149 • kidney problems
- bleeding problems

- 150 • alcoholism
- 151 • drug abuse or addiction
- 152 • body organ transplant and are taking medicine that keeps your body from
- 153 rejecting your transplant (suppresses your immune system).
- 154 • high blood triglycerides (fat particles normally found in your blood)

155

156 How should I take INTRON® A?

157

158 To get the most benefit from this medicine, it is important that you take INTRON® A
159 exactly as your healthcare provider tells you. Your healthcare provider will decide
160 your dose of INTRON® A and how often you will take it. Do not take more than your
161 prescribed dose. INTRON® A is given as an injection either under the skin
162 (subcutaneous) or into a muscle (intramuscular). You should be completely
163 comfortable with how to prepare and measure your dose of INTRON® A and how to
164 inject yourself before you use INTRON® A for the first time. Your healthcare provider
165 will train you on how to use and inject INTRON® A properly.

166

167 INTRON® A comes in different strengths and different forms (a powder in a vial, a
168 solution in a vial and a multidose pen). Your healthcare provider will determine which
169 form is best for you. The instructions for giving a dose of INTRON® A are at the end
170 of this leaflet.

171

172 If you miss a dose of INTRON® A, take the missed dose as soon as possible during
173 the same day or the next day, then continue on your regular dosing schedule. If
174 several days go by after you miss a dose, check with your healthcare provider to see
175 what to do. **Do not double your next dose** or take more than your prescribed dose
176 without talking to your healthcare provider. Call your healthcare provider right away if
177 you take more than your prescribed dose. Your healthcare provider may wish to
178 examine you more closely and take blood for testing.

179

180 If you are taking INTRON® A in combination with REBETOL®, you should also read
181 the Medication Guide for REBETOL® (ribavirin, USP) for more information about
182 side effects and how to take REBETOL®. **REBETOL® capsules should be taken**
183 **twice a day with food.** Taking REBETOL® with food helps your body take up more
184 of the medicine. Taking REBETOL® at the same time of day every day will help
185 keep the amount of medicine in your body at a steady level. This can help your
186 healthcare provider decide how your treatment is working and how to change the
187 number of REBETOL® capsules you take if you have side effects. If you miss a
188 dose of REBETOL®, take the missed dose as soon as possible during the same
189 day. If an entire day has passed, check with your healthcare provider about what to
190 do. **Do not double your next dose.**

191 You must see your healthcare provider on a regular basis for blood tests so your
192 healthcare provider can check how the treatment is working for you and to check for
193 side effects.

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195 Tell your healthcare provider if you are taking or planning to take other prescription
196 or non-prescription medicines, including vitamin and mineral supplements and
197 herbal medicines.

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What should I avoid while taking INTRON® A?

- 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 cause you to lose your baby (miscarry). If you or your partner becomes pregnant during treatment or during the 6 months after treatment with INTRON® A/REBETOL® combination therapy, immediately report the pregnancy to your healthcare provider. Your healthcare provider will make decisions about your treatment. Your healthcare provider should call 1-800-593-2214. Your healthcare provider will be asked to give follow-up information about the pregnancy.
- Do not breast-feed your baby while taking INTRON® A.

What are the possible side effects of INTRON® A?

Possible, serious side effects include:

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

Common but less serious side effects include:

- **Flu-like symptoms.** Most patients who take INTRON® A have "flu-like" symptoms (headache, muscle aches, tiredness, and fever) that usually lessen after the first few weeks of therapy. You can reduce some of these symptoms by injecting your INTRON® A dose at bedtime. Over-the-counter pain and fever medications can be used to prevent or reduce the fever and headache. If your fever does not go away you should tell your healthcare provider.
- **Extreme fatigue (tiredness).** Many patients become extremely tired while on INTRON® A.
- **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.
- **Blood sugar problems.** Some patients develop problems with the way their body controls their blood sugar and may develop high blood sugar or diabetes.

- 245 • **Skin reactions.** Redness, swelling, and itching are common at the site of
246 injection. If after several days these symptoms do not disappear, contact your
247 healthcare provider. You may get a rash during therapy. If this occurs, your
248 healthcare provider may recommend medicine to treat the rash.
249 • **Hair thinning.** Hair thinning is common during INTRON® A treatment. Hair loss
250 stops and hair growth returns after therapy is stopped.

251
252 These are not all the side effects of INTRON® A or INTRON® A/REBETOL®
253 combination therapy. Your healthcare provider can give you a more complete list.
254

255 **General advice about prescription medicines**

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

261
262 This Medication Guide has been approved by the U.S. Food and Drug
263 Administration.

264
265 Manufactured by: Schering Corporation Kenilworth, NJ 07033 USA

266
267 Issued: July 2007

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269 *Safety-Lok is a trademark of Becton Dickinson and Company

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275 **Medication Guide Appendix: Instructions for Preparing and Giving a Dose of** 276 **INTRON® A Powder for Injection**

- 277
278 • INTRON® A medication has been supplied to you as a powder form that requires
279 you to add the supplied liquid (DILUENT) to the powder. The liquid (DILUENT) is
280 supplied to you in a vial.

281
282 **The INTRON® A Powder for Injection may be supplied to you in 10 million IU,**
283 **18 million IU, or 50 million IU vials.** These packages contain 1 vial of INTRON® A
284 powder and 1 vial of DILUENT (Sterile Water for Injection, USP). Syringes are not
285 supplied to you. Talk to your healthcare provider about what syringes you should
286 use

287 288 **Storing INTRON® A Powder for Injection**

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

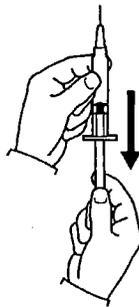
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NOTE: INTRON® A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.

296 **Preparing a Dose of INTRON® A Powder for Injection**

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1. Find a well lit, clean, flat working surface such as a table. Collect the supplies you will need for an injection:
 - 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
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.
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.
4. Gently warm the DILUENT vial by slowly rolling the vial in the palms of your hands for one minute.
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.
6. Open the syringe package and remove the syringe.
7. Remove the needle cover from the syringe. Fill the syringe with air by pulling the plunger back to the mark on the syringe that matches the dose prescribed by your healthcare provider.

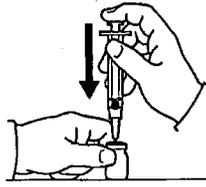


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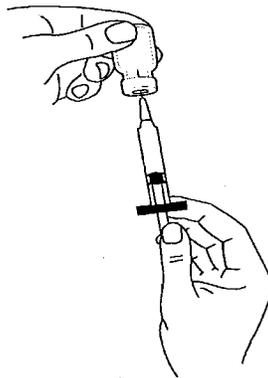
8. Hold the DILUENT vial on your flat working surface without touching the cleaned rubber stopper with your hands.

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

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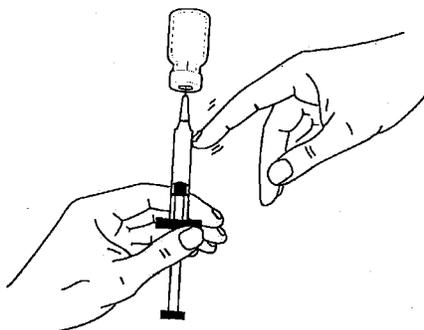


10. Keep the needle in the vial and turn the vial upside down. Make sure the tip of the needle is in the DILUENT. Slowly pull the plunger back to fill the syringe with DILUENT to the number (mL or cc) that your healthcare provider instructed you to use.



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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.



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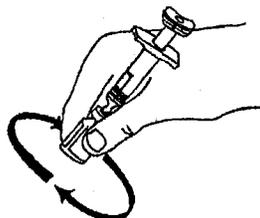
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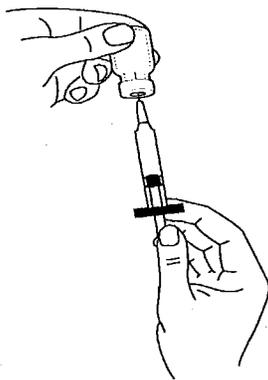
17. Check the solution inside the vial of the INTRON® A. The solution should be clear and colorless to light yellow, without particles. Do not use the INTRON® A

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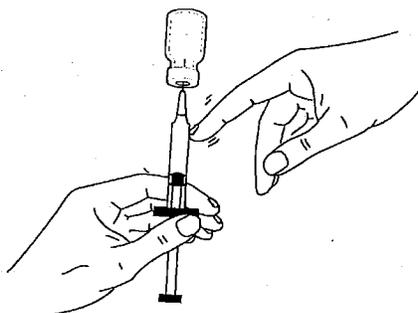
406 if the medicine is cloudy, has particles or is any color besides clear and colorless
407 to light yellow.

408 18. With the needle in the vial, turn the vial upside down. Make sure the tip of the
409 needle is in the INTRON® A solution. Slowly pull the plunger back to fill the
410 syringe with the INTRON® A solution to the number (mL or cc) that your
411 healthcare provider has prescribed.
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417 19. With the needle still inserted in the vial, check the syringe for air bubbles. If there
418 are any air bubbles, gently tap the syringe with your finger until the air bubbles
419 rise to the top of the syringe.
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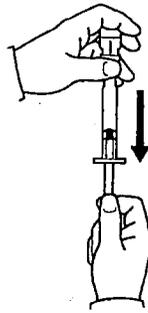


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20. Slowly push the plunger up to remove the air bubbles. If you push solution back
into the vial, slowly pull back on the plunger again to draw the correct amount of
INTRON® A solution back into the syringe.

21. 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.

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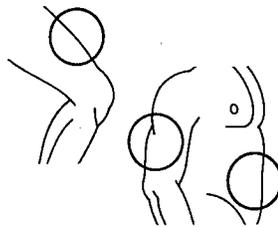
Choosing an Injection site

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.

FOR SUBCUTANEOUS INJECTION

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

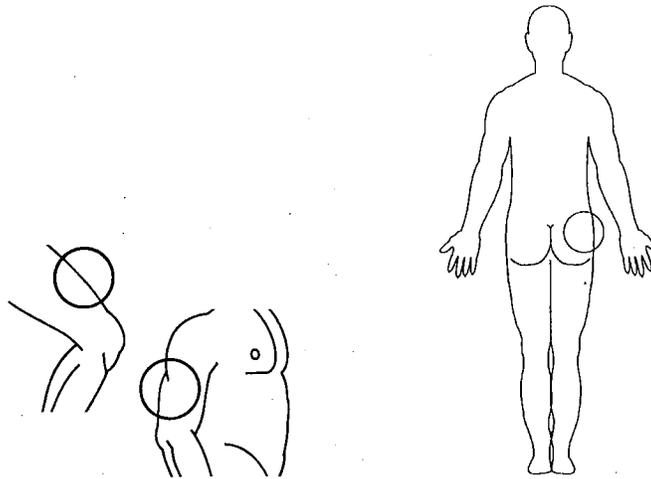


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FOR INTRAMUSCULAR INJECTION

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.

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 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:

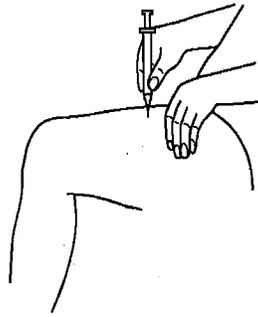
- 4a. Hold the syringe (like a pencil) at a **45-degree angle** to the skin. With a quick “dart-like” motion push the needle into the skin.



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

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 those 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

541 use a hard plastic container with a screw-on cap (like a laundry detergent
542 container).
543 • DO NOT use glass or clear plastic containers for disposal of needles and
544 syringes.
545

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

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

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MEDICATION GUIDE

INTRON® A

(Interferon alfa-2b, recombinant)

Including appendix with instructions for using INTRON A Solution for Injection

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

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

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

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

You should call your healthcare provider immediately if you develop any of these conditions while taking INTRON A:

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

The most serious possible side effects of INTRON A include:

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 healthcare provider 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 healthcare provider right away. **There is a Ribavirin
65 Pregnancy Registry that collects information about pregnancy outcomes in
66 female patients and female partners of male patients exposed to ribavirin. You
67 or your healthcare provider are encouraged to contact the Registry at 1-800-
68 593-2214.**

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

80
81 **Eye problems.** If you notice any changes in your eyesight such as difficulty seeing,
82 it could mean that your eyes are being affected, so you should call your healthcare
83 provider right away.

84
85 **Heart problems.** Some patients taking INTRON A may develop problems with their
86 heart, including low blood pressure, fast heart rate, and very rarely, heart attacks.
87 Tell your healthcare provider if you have had any heart problems in the past.

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

93
94 If you are taking INTRON A and REBETOL combination therapy, REBETOL can
95 cause a drop in your number of red blood cells (anemia). A very low red blood cell
96 count can be dangerous especially if you have heart or breathing problems.

97 For other possible side effects of INTRON A. see *"What are the possible side*
98 *effects of INTRON A?" in this Medication Guide.*

99 **What is INTRON A?**

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

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

108
109 It is also not known if INTRON A or INTRON A/REBETOL combination therapy will
110 prevent one infected person from infecting another person with hepatitis B or C.

111
112 **Who should not take INTRON A?**

113
114 Do not take the INTRON A alone or in combination with REBETOL if you:

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

125
126 **If you have any of the following conditions or serious medical problems, tell**
127 **your healthcare provider before taking INTRON A alone or in combination with**
128 **REBETOL:**

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

- 146 • alcoholism
- 147 • drug abuse or addiction
- 148 • body organ transplant and are taking medicine that keeps your body from
- 149 rejecting your transplant (suppresses your immune system).
- 150 • high blood triglycerides (fat particles normally found in your blood)

151

152 How should I take INTRON A?

153

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

162

163 INTRON A comes in different strengths and different forms (a powder in a vial, a
164 solution in a vial and a multidose pen). Your healthcare provider will determine which
165 form is best for you. The instructions for giving a dose of INTRON A are at the end of
166 this leaflet.

167

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

175

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

187 You must see your healthcare provider on a regular basis for blood tests so your
188 healthcare provider can check how the treatment is working for you and to check for
189 side effects.

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191 Tell your healthcare provider if you are taking or planning to take other prescription
192 or non-prescription medicines, including vitamin and mineral supplements and
193 herbal medicines.

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What should I avoid while taking INTRON A?

- Avoid becoming pregnant while taking INTRON A. INTRON A alone and INTRON A taken in combination with REBETOL may harm your unborn child or cause you to lose your baby (miscarry). If you or your partner becomes pregnant during treatment or during the 6 months after treatment with INTRON A/REBETOL combination therapy, immediately report the pregnancy to your healthcare provider. Your healthcare provider will make decisions about your treatment. Your healthcare provider should call 1-800-593-2214. Your healthcare provider will be asked to give follow-up information about the pregnancy.
- Do not breast-feed your baby while taking INTRON A.

What are the possible side effects of INTRON A?

Possible, serious side effects include:

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

Common but less serious side effects include:

- **Flu-like symptoms.** Most patients who take INTRON A have "flu-like" symptoms (headache, muscle aches, tiredness, and fever) that usually lessen after the first few weeks of therapy. You can reduce some of these symptoms by injecting your INTRON A dose at bedtime. Over-the-counter pain and fever medications can be used to prevent or reduce the fever and headache. If your fever does not go away you should tell your healthcare provider.
- **Extreme fatigue (tiredness).** Many patients become extremely tired while on INTRON A.
- **Appetite problems.** Nausea, loss of appetite, and weight loss, occur commonly.
- **Blood sugar problems.** Some patients develop problems with the way their body controls their blood sugar and may develop high blood sugar or diabetes.

- 242 • **Skin reactions.** Redness, swelling, and itching are common at the site of
243 injection. If after several days these symptoms do not disappear, contact your
244 healthcare provider. You may get a rash during therapy. If this occurs, your
245 healthcare provider may recommend medicine to treat the rash.
246
- 247 • **Hair thinning.** Hair thinning is common during INTRON A treatment. Hair loss
248 stops and hair growth returns after therapy is stopped.
249

250 These are not all the side effects of INTRON A or INTRON A/REBETOL combination
251 therapy. Your healthcare provider can give you a more complete list.
252

253 **General advice about prescription medicines**

254 Medicines are sometimes prescribed for purposes other than those listed in a
255 Medication Guide. If you have any concerns about the INTRON A product, you're
256 your healthcare provider. Your health care provider can give you additional
257 information about INTRON A. Do not use INTRON A for a condition for which it was
258 not prescribed. Do not share this medication with other people.
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261 This Medication Guide has been approved by the U.S. Food and Drug
262 Administration.
263

264 Manufactured by: Schering Corporation Kenilworth, NJ 07033 USA
265

266 Issued: July 2007
267

268 *Safety-Lok is a trademark of Becton Dickinson and Company
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274 **Medication Guide Appendix: Instructions for Preparing and Giving a Dose of** 275 **INTRON A Solution for Injection** 276

- 277 • INTRON A medication has been supplied to you in a liquid form in a vial.
278

279 **The INTRON A Solution for Injection may be supplied to you as either:**
280

- 281 • **INTRON A Solution in a Pak-10 (10 million IU) package.** This package
282 contains 6 single-use INTRON A vials of solution, 6 single-use disposable
283 Safety-Lok* syringes, and 12 alcohol swabs.
284

- 285 • **INTRON A Solution 18 million IU and 25 million IU multidose vial.** These
286 packages contain 1 vial of INTRON A solution. Syringes are not supplied to you.
287 Talk to your healthcare provider about what syringes you should use.
288

289 **Storing INTRON A Solution for Injection**

290 INTRON A Solution for Injection should be stored in the refrigerator between 2° and
291 8°C (36° and 46°F). **DO NOT FREEZE.** If you are using the Pak-10, 10 Million IU
292 single use vials discard any unused INTRON A solution remaining after use. If you
293 are using the 18 or 25 million IU multidose vials discard any unused INTRON A
294 solution remaining after one month.

295

296 **Preparing a Dose of INTRON A Solution for Injection**

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

300

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- A vial of INTRON A solution
- A single-use disposable Safety-Lok* syringe (provided in the "Pak-10") only,
or a syringe you have obtained for use with the multi-use vials
- A cotton ball or gauze
- Two alcohol swabs
- A puncture-proof disposable container

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

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312 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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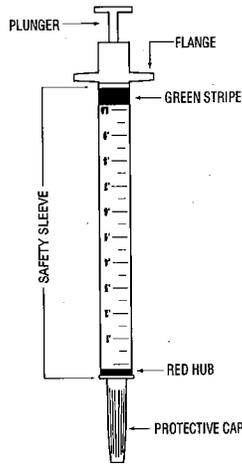
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If you are using the multidose vials, open the package for the syringe you are using
and if it does not have a needle attached, then attach one of the needles you have
obtained to the syringe.

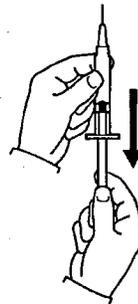
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9. Remove the protective cap from the needle of the syringe. Fill the syringe with air by pulling the plunger back to the mark on the syringe that matches the dose as prescribed by your healthcare provider.

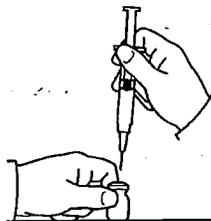
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10. Hold the vial of INTRON A Solution for Injection on your flat working surface without touching the cleaned rubber stopper with your hands.

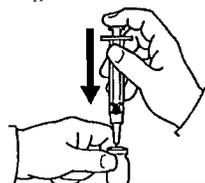
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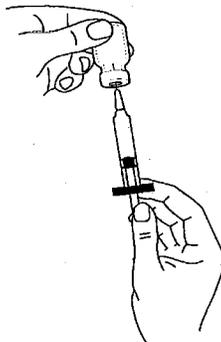
11. Insert the needle straight down through the middle of the rubber stopper of the vial containing the INTRON A solution. Slowly inject all the air from the syringe into the air space above the solution.

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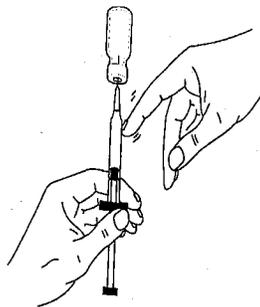
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12. Keep the needle in the vial and turn the vial upside down. Make sure the tip of the needle is in the INTRON A solution. Slowly pull the plunger back to fill the syringe with INTRON A solution to the number (mL or cc) as prescribed by your healthcare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

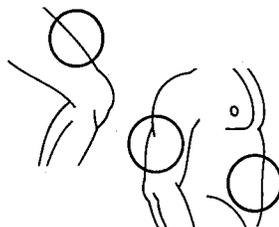
Based on your treatment, your healthcare provider will tell you if you should inject a dose of INTRON A subcutaneously (under the skin) or intramuscularly (into the muscle). If it is too difficult for you to inject, ask someone who has been trained to give injections to help you.

FOR SUBCUTANEOUS INJECTION

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

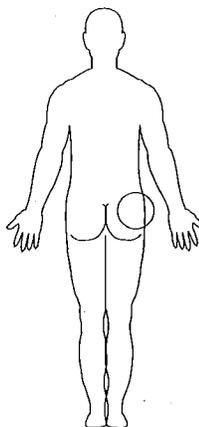
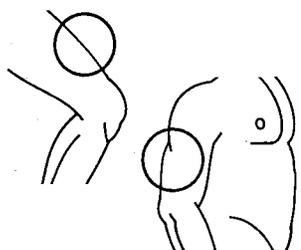


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FOR INTRAMUSCULAR INJECTION

The best sites for injection into your muscle are:

- the front of the middle thighs
- the 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.

Injecting the Dose of INTRON A

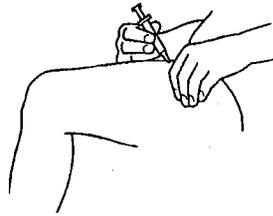
1. Clean the injection site with a new alcohol swab.
2. Pick up the vial and syringe from your flat work surface. Remove the syringe and needle from the vial. Hold the syringe in the hand that you will use to inject INTRON A. Do not touch the needle or allow it to touch the work

431 surface. If you are using a Safety-Lok* syringe, make sure the safety sleeve
432 is pushed against the syringe flange so that the needle is fully exposed.
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434 3. With your free hand, pinch a fold of the skin at the cleaned injection site.
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436 **FOR SUBCUTANEOUS INJECTION:**
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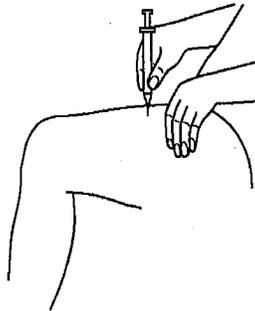
438 4b. Hold the syringe (like a pencil) at a **45-degree angle** to the skin. With a quick
439 "dart-like" motion, push the needle into the skin.
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455 **FOR INTRAMUSCULAR INJECTION:**
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457 4b. Hold the syringe (like a pencil) at a **90-degree angle** to the skin. With a
458 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 and prepare a new injection site.

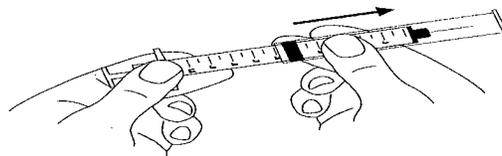
6. If no blood is present in the syringe, inject the medicine by gently pushing the plunger all the way down until the syringe is empty.

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

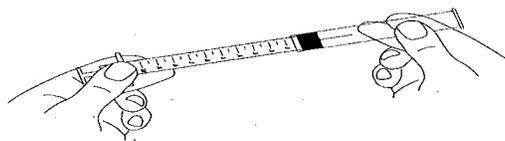
488 There may be special state and local laws for disposal of used needles and
489 syringes. Your healthcare provider should provide you with instructions on how to
490 properly dispose of your used syringes and needles. Always follow those
491 instructions. The instructions below should be used as a general guide for proper
492 disposal.
493

- 494 • **The needles and syringes should never be reused**
495
496 • **Disposing of the Safety-Lok* syringe.** To dispose of the Safety-Lok* syringe,
497 hold the flange of the syringe with one hand. Grasp the safety sleeve with your
498 free hand, sliding it completely over the needle. The green stripe on the safety
499 sleeve should cover the red hub of the needle and fit snugly.
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- 505 • Place all used needles and syringes in a puncture-proof disposable container
506 that is available through your pharmacy or healthcare provider. You may also use
507 a hard plastic container with a screw-on cap (like a laundry detergent container).
508 DO NOT use glass or clear plastic containers for disposal of needles and
509 syringes.

- 510 • The container used for the disposal of syringes, needles, and Safety-Lok*
511 syringes should be clearly labeled as "USED SYRINGES AND NEEDLES."
512 When the container is almost full, tighten the lid. Tape the cap or lid to make
513 sure it does not come off. Dispose of the container as instructed by your
514 healthcare provider.
515 DO NOT throw the container in your household trash and DO NOT recycle.
516
517 • **Always keep the container out of reach of children.**

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MEDICATION GUIDE

INTRON[®] A

(Interferon alfa-2b, recombinant)

Including appendix with instructions for using INTRON A Multidose Pen for Injection

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

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

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

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

You should call your healthcare provider immediately if you develop any of these conditions while taking INTRON A:

- you become pregnant or if you are a male and your female partner becomes pregnant
- new or worsening mental health problems such as thoughts about hurting or killing yourself or others
- decreased vision
- trouble breathing or chest pain
- severe stomach or lower back pain
- bloody diarrhea or bloody bowel movements
- high fever
- easy bruising or bleeding

The most serious possible side effects of INTRON A include:

RISK TO PREGNANCY. Combination INTRON A and REBETOL therapy can cause death, serious birth defects or other harm to your unborn child. If you are pregnant, you or your male partner must not take INTRON A and REBETOL combination therapy. You must not become pregnant while either you or your partner are taking the combination of INTRON A and REBETOL and for 6 months after you stop taking the combination. If you are a woman of childbearing age you must have negative pregnancy tests immediately before starting treatment, during treatment and for 6 months after you have stopped treatment. You should use two forms of birth control during and for 6 months after you have stopped treatment. If you are a man taking INTRON A/REBETOL combination therapy, one of the two forms of birth control should be a condom. You must use birth control even if you believe that you are not fertile or that your fertility is low. You should talk to your healthcare provider about birth control for you and your partner. If you or your partner becomes pregnant while either of you is being treated or within 6 months of stopping treatment tell your healthcare provider right away. **There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes in female patients and female partners of male patients exposed to ribavirin. You or your healthcare provider are encouraged to contact the Registry at 1-800-593-2214.**

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

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

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

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

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

For other possible side effects of INTRON A, see "What are the possible side effects of INTRON A?" in this Medication Guide.

What is INTRON A?

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

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

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

Who should not take INTRON A?

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

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

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

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

How should I take INTRON A?

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

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

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

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

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

Tell your healthcare provider if you are taking or planning to take other prescription or non-prescription medicines, including vitamin and mineral supplements and herbal medicines.

What should I avoid while taking INTRON A?

- Avoid becoming pregnant while taking INTRON A. INTRON A alone and INTRON A taken in combination with REBETOL may harm your unborn child or cause you to lose your baby (miscarry). If you or your partner becomes pregnant during treatment or during the 6 months after treatment with INTRON A/REBETOL combination therapy, immediately report the pregnancy to your healthcare provider. Your healthcare provider will make decisions about your treatment. Your healthcare provider should call 1-800-593-2214. Your healthcare provider will be asked to give follow-up information about the pregnancy.
- Do not breast-feed your baby while taking INTRON A.

What are the possible side effects of INTRON A?

Possible, serious side effects include:

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

Common but less serious side effects include:

- **Flu-like symptoms.** Most patients who take INTRON A have "flu-like" symptoms (headache, muscle aches, tiredness, and fever) that usually lessen after the first few weeks of therapy. You can reduce some of these symptoms by injecting your INTRON A dose at bedtime. Over-the-counter pain and fever medications can be used to prevent or reduce the fever and headache. If your fever does not go away you should tell your healthcare provider.
- **Extreme fatigue (tiredness).** Many patients become extremely tired while on INTRON A.

- **Appetite problems.** Nausea, loss of appetite, and weight loss occur commonly.
- **Blood sugar problems.** Some patients develop problems with the way their body controls their blood sugar and may develop high blood sugar or diabetes.
- **Skin reactions.** Redness, swelling, and itching are common at the site of injection. If after several days these symptoms do not disappear, contact your healthcare provider. You may get a rash during therapy. If this occurs, your healthcare provider may recommend medicine to treat the rash.
- **Hair thinning.** Hair thinning is common during INTRON A treatment. Hair loss stops and hair growth returns after therapy is stopped.

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

General advice about prescription medicines

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

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

Manufactured by: Schering Corporation Kenilworth, NJ 07033 USA

Issued: 1/07

Instructional leaflet and video are available through your healthcare provider.

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Rev. 1/07

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

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

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

- 3 Million International Units (MIU) with a brown push button and a brown color-coding strip. The different doses that it can deliver are 1.5 MIU, 3.0 MIU, 4.5

MIU, and 6.0 MIU. Six MIU is the maximum dose that this pen can deliver at one time.

- 5 Million International Units (MIU) with a light blue push button and a light blue color-coding strip. The different doses that it can deliver are 2.5 MIU, 5.0 MIU, 7.5 MIU, and 10.0 MIU. Ten MIU is the maximum dose that this pen can deliver at one time.
- 10 Million International Units (MIU) with a pink push button and a pink color-coding strip. The different doses that it can deliver are 5.0 MIU, 10.0 MIU, 15.0 MIU, and 20.0 MIU. Twenty MIU is the maximum dose that this pen can deliver at one time.

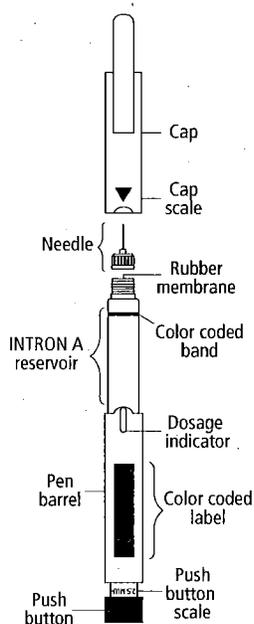
Make sure that you have the correct INTRON A multidose pen as prescribed by your healthcare provider.

Description of your INTRON A multidose pen

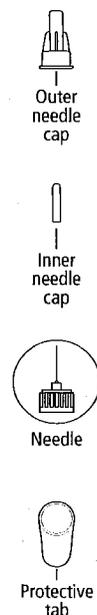
- The INTRON A multidose pen should **ONLY** be used with **Novofine*** needles. These are the needles that come packaged with the pen. If you use other needles the pen may not work properly and you could get the wrong dose of INTRON A.

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:

INTRON A Pen



Novofine Needle Assembly



- 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.
- 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.
- 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.

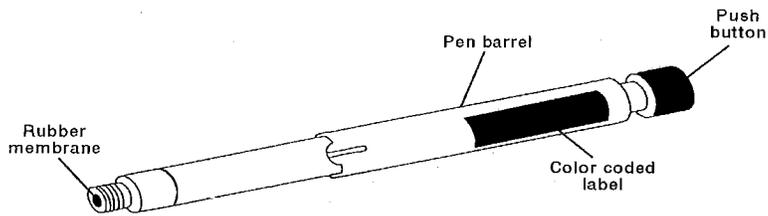
To avoid the possible transmission of disease, do not allow anyone else to use your multidose pen.

Storing INTRON A Solution Multidose Pen for Injection

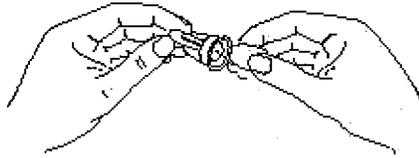
INTRON A Solution Multidose Pen for Injection should be stored in the refrigerator between 2° and 8°C (36° and 46°F). Discard any unused INTRON A pen remaining after four weeks. **DO NOT FREEZE.**

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

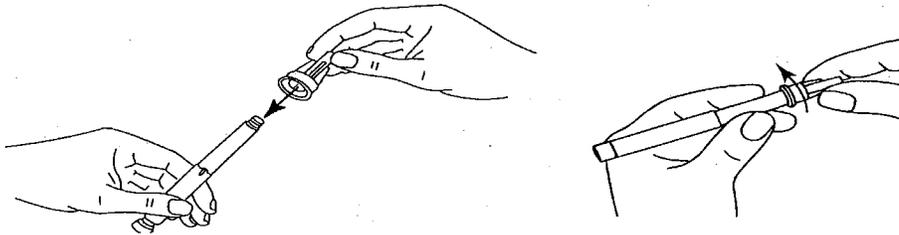
1. Find a well-lit, clean, flat working surface such as a table. Collect the supplies you will need for an injection:
 - the intron a multidose pen
 - two alcohol swabs
 - a cotton ball or gauze
 - a puncture-proof disposable container
2. Before removing the multidose pen from the carton, check the date 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.
4. Remove the multidose pen from the carton. Pull the cap off the pen and wipe the rubber membrane with one alcohol swab.



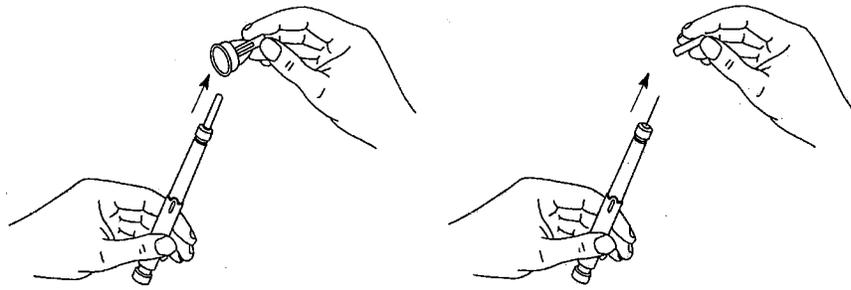
5. Check the solution inside the pen. The solution should be clear and colorless, without particles. Do not use the INTRON A if the medicine is cloudy, has particles, or is any color besides clear and colorless.
6. Remove the paper backing from the Novofine needle by pulling the paper tab. You will see the back of the needle once the paper tab is removed.



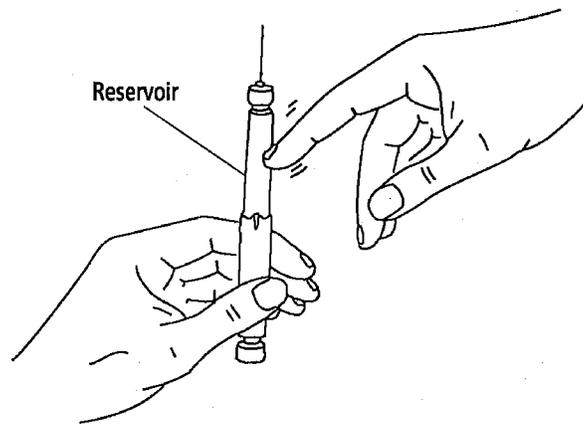
7. Keep the needle in its outer clear needle cap and gently push the Novofine needle straight into the pen's rubber membrane you just cleaned. Screw the needle onto the INTRON A multidose pen by turning it clockwise.



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.



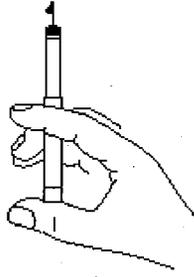
9. Keep the needle facing up and remove any air bubbles that may be in the reservoir by tapping the reservoir with your finger. If you have any air bubbles, they will rise to the top of the reservoir.



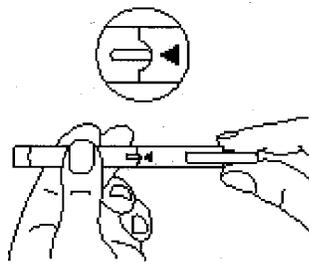
10. Hold the pen by the barrel and turn the INTRON A reservoir clockwise until you feel it click into place.



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.

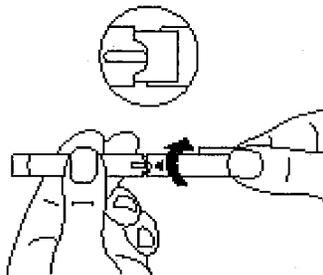
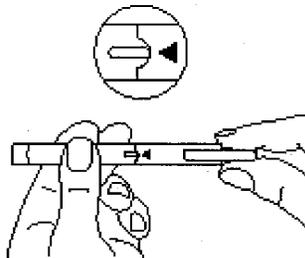


12. Place the cap back on the INTRON A multidose pen. Make sure you line up the black triangle on the pen cap with the dosage indicator on the pen barrel. The pen is now ready to set the dose.



Setting the dose prescribed by your healthcare provider

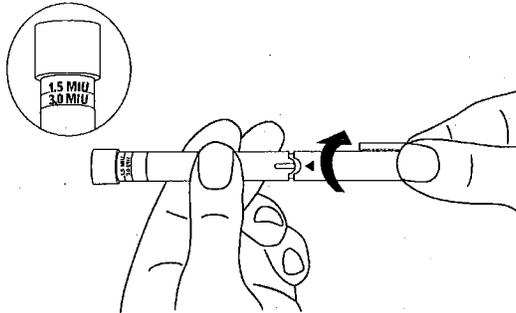
13. Hold the pen horizontally in the middle of the pen barrel so the push button can move freely. With the other hand, hold the multidose pen cap.



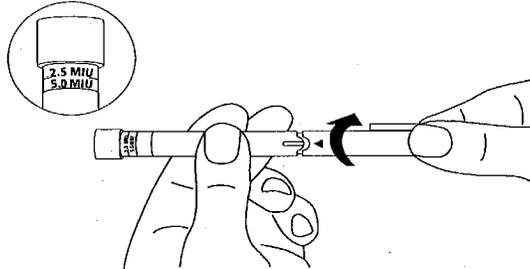
14. Set the dose prescribed by your healthcare provider by turning the cap clockwise. With each clockwise turn, the push button will start to rise and you will

see the push button scale. Do not use force to turn the pen cap or you may damage the pen.

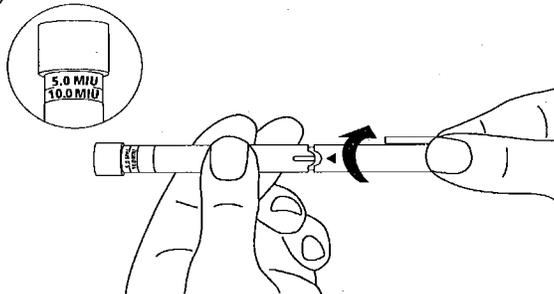
- To set a 3.0 MIU dose using the 3 MIU multidose pen, turn the cap 2 full turns (10 clicks) = 3.0 MIU.



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



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



15. After each complete turn, make sure the triangle on the cap is lined up with the dosage indicator on the pen barrel.

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

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

1 full turn (5 clicks) = 1.5 MIU

3 full turns (15 clicks) = 4.5 MIU

4 full turns (20 clicks) = 6.0 MIU

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

1 full turn (5 clicks) = 2.5 MIU

3 full turns (15 clicks) = 7.5 MIU

4 full turns (20 clicks) = 10.0 MIU

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

1 full turn (5 clicks) = 5.0 MIU

3 full turns (15 clicks) = 15.0 MIU

4 full turns (20 clicks) = 20.0 MIU

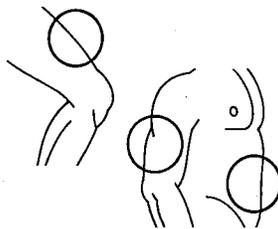
16. Check the push button scale to make sure you have set the correct dose.
17. If you have set a wrong dose, turn the cap back (counterclockwise) as far as you can until the push button is all the way in and the push button scale is completely covered, then begin at step 12 again.
18. Gently warm the 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.
19. Place the multidose pen on your flat work surface until you are ready to inject INTRON A.

Choosing an Injection Site

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.

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

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



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 your dose of INTRON A

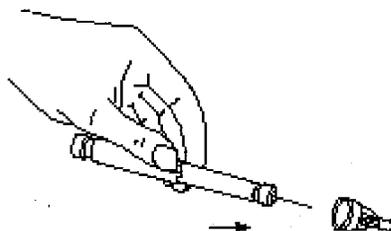
1. Clean the injection site with a new alcohol swab.
2. Pick up the multidose pen from your flat work surface and remove the cap from the needle.
3. With one hand, pinch a fold of the skin at the cleaned injection site.
4. With the other hand, hold the multidose pen (like a pencil) at a **45 degree angle**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



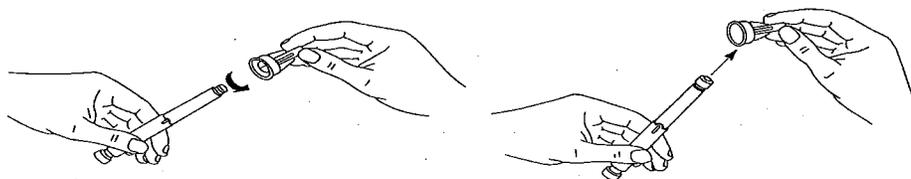
5. After the needle is in, remove the hand used to pinch the skin and use it to hold the pen barrel. If blood comes into the pen reservoir, the needle has entered a blood vessel. **Do not inject INTRON A.** Withdraw the needle and discard the used multi-dose pen in the puncture-proof container. Contact your healthcare provider. Repeat the steps to prepare for an injection.
6. If no blood is present in the pen reservoir, inject the medicine by gently pressing the push button all the way down.
7. Leave the needle in place for a few seconds while holding down the push button.
8. Slowly release the push button and pull the needle out of the skin.
9. 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.
10. 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

Removing the needle from the multidose pen

11. Using a scooping motion, carefully replace the outer clear needle cap (like capping a pen).

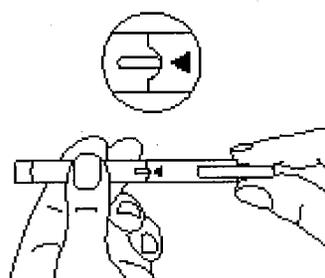


12. Once capped, remove the needle by holding the clear outer needle cap with one hand and holding the pen barrel with the other hand, turning counterclockwise.



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.



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 4 weeks.

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

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

- The needles should never be reused.
- Place all used needles and multidose pens in a puncture-proof disposable container that is available through your pharmacy or healthcare provider. You may use a hard plastic container with a screw-on cap (like a laundry detergent container). DO NOT use glass or clear plastic containers for disposal of needles.
- The container should be clearly labeled as "USED NEEDLES AND MULTIDOSE PENS." When the container is about two-thirds full, dispose of the container as instructed by your healthcare provider. DO NOT throw the container in your household trash. DO NOT recycle.
- **Always keep the container out of the reach of children.**

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Schering Corporation

Kenilworth, NJ 07033

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