

1 **PRODUCT**
 2 **INFORMATION**
 3 **INTRON® A**
 4 **Interferon alfa-2b,**
 5 **recombinant**
 6 **For Injection**

8 **WARNING**

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 13 withdrawn from therapy.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

16 **DESCRIPTION**

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

19 INTRON A recombinant for Injection has been classified as an alpha interferon
 20 and is a water-soluble protein with a molecular weight of 19,271 daltons produced by
 21 recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of
 22 *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-
 23 2b gene from human leukocytes. The fermentation is carried out in a defined nutrient
 24 medium containing the antibiotic tetracycline hydrochloride at a concentration of 5 to 10
 25 mg/L; the presence of this antibiotic is not detectable in the final product. The specific
 26 activity of interferon alfa-2b, recombinant is approximately 2.6×10^8 IU/mg protein as
 27 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.

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

32

Solution Vials for Injection

Vial Strength	Concentration*	mg INTRON A [†] per vial	Route of Administration
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).

33

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
3 MIU	22.5	3 MIU/0.2 mL	0.087	SC
5 MIU	37.5	5 MIU/0.2 mL	0.144	SC
10 MIU	75	10 MIU/0.2 mL	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.

34

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

37

38 CLINICAL PHARMACOLOGY

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

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

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

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

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

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

65 After intravenous administration, serum INTRON A concentrations peaked (135-
66 273 IU/mL) by the end of the 30-minute infusion, then declined at a slightly more rapid
67 rate than after intramuscular or subcutaneous drug administration, becoming
68 undetectable 4 hours after the infusion. The elimination half-life was approximately 2
69 hours.

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

74 There are no pharmacokinetic data available for the intralesional route of
75 administration.

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

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

96

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

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

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

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

134

135 **Malignant Melanoma** The safety and efficacy of INTRON A was evaluated as adjuvant
136 to surgical treatment in patients with melanoma who were free of disease (post surgery)
137 but at high risk for systemic recurrence. These included patients with lesions of Breslow
138 thickness greater than 4 mm, or patients with lesions of any Breslow thickness with
139 primary or recurrent nodal involvement. In a randomized, controlled trial in 280 patients,
140 143 patients received INTRON A therapy at 20 million IU/m² intravenously five times per
141 week for 4 weeks (induction phase) followed by 10 million IU/m² subcutaneously three

142 times per week for 48 weeks (maintenance phase). In the clinical trial, the median daily
143 INTRON A dose administered to patients was 19.1 million IU/m² during the induction
144 phase and 9.1 million IU/m² during the maintenance phase. INTRON A therapy was
145 begun less than or equal to 56 days after surgical resection. The remaining 137
146 patients were observed.

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

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

165
166 **Follicular Lymphoma** The safety and efficacy of INTRON A in conjunction with CHVP,
167 a combination chemotherapy regimen, was evaluated as initial treatment in patients with
168 clinically aggressive, large tumor burden, Stage III/IV follicular Non-Hodgkin's
169 Lymphoma. Large tumor burden was defined by the presence of any one of the
170 following: a nodal or extranodal tumor mass with a diameter of greater than 7 cm;
171 involvement of at least three nodal sites (each with a diameter of greater than 3 cm);
172 systemic symptoms; splenomegaly; serous effusion, orbital or epidural involvement;
173 ureteral compression; or leukemia.

174 In a randomized, controlled trial, 130 patients received CHVP therapy and
175 135 patients received CHVP therapy plus INTRON A therapy at 5 million IU
176 subcutaneously three times weekly for the duration of 18 months. CHVP chemotherapy
177 consisted of cyclophosphamide 600 mg/m², doxorubicin 25 mg/m², and teniposide (VM-
178 26) 60 mg/m², administered intravenously on Day 1 and prednisone at a daily dose of
179 40 mg/m² given orally on Days 1 to 5. Treatment consisted of six CHVP cycles
180 administered monthly, followed by an additional six cycles administered every 2 months
181 for 1 year. Patients in both treatment groups received a total of 12 CHVP cycles over
182 18 months.

183 The group receiving the combination of INTRON A therapy plus CHVP had a
184 significantly longer progression-free survival (2.9 years vs 1.5 years, $P=0.0001$, Log
185 Rank test). After a median follow-up of 6.1 years, the median survival for patients
186 treated with CHVP alone was 5.5 years while median survival for patients treated with
187 CHVP plus INTRON A therapy had not been reached ($P=0.004$, Log Rank test). In

188 three additional published, randomized, controlled studies of the addition of interferon
189 alpha to anthracycline-containing combination chemotherapy regimens,¹⁻³ the addition
190 of interferon alpha was associated with significantly prolonged progression-free survival.
191 Differences in overall survival were not consistently observed.

192

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

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

210 In one of these studies, 43% (54/125) of patients in whom multiple (less than or
211 equal to 3) lesions were treated experienced complete clearing of all treated lesions
212 during the course of the study. Of these patients, 81% remained cleared 16 weeks after
213 treatment was initiated.

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

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

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

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

234

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

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

243 Forty-four percent of asymptomatic patients responded vs 7% of symptomatic
244 patients. The median time to response was approximately 2 months and 1 month,
245 respectively, for asymptomatic and symptomatic patients. The median duration of
246 response was approximately 3 months and 1 month, respectively, for the asymptomatic
247 and symptomatic patients. Baseline T4/T8 ratios were 0.46 for responders vs 0.33 for
248 nonresponders.

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

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

261 In the 30 million IU study group, 7% (5/72) of patients were complete responders
262 and 22% (16/72) of the patients were partial responders. The 35 million IU study had
263 13% (3/23 patients) complete responders and 17% (4/23) partial responders.

264 For patients who received 30 million IU TIW, the median survival time was longer
265 in patients with CD4 greater than 200 (30.7 months) than in patients with CD4 less than
266 or equal to 200 (8.9 months). Among responders, the median survival time was 22.6
267 months vs 9.7 months in nonresponders.

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

279 Two additional studies have investigated longer treatment durations (up to
280 24 months).^{5,6} Patients in the two studies to evaluate longer duration of treatment had
281 hepatitis with or without cirrhosis in the absence of decompensated liver disease.
282 Complete response to treatment was defined as normalization of the final two serum
283 ALT levels during the treatment period. A sustained response was defined as a
284 complete response at the end of the treatment period, with sustained normal ALT
285 values lasting at least 6 months following discontinuation of therapy.

286 In Study 1, all patients were initially treated with INTRON A 3 million IU TIW
287 subcutaneously for 24 weeks (run-in-period). Patients who completed the initial
288 24-week treatment period were then randomly assigned to receive no further treatment,
289 or to receive 3 million IU TIW for an additional 48 weeks. In Study 2, patients who met
290 the entry criteria were randomly assigned to receive INTRON A 3 million IU TIW
291 subcutaneously for 24 weeks or to receive INTRON A 3 million IU TIW subcutaneously
292 for 96 weeks. In both studies, patient follow-up was variable and some data collection
293 was retrospective.

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

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

309 Combination treatment with INTRON A and REBETOL[®] (ribavirin USP) provided
310 a significant reduction in virologic load and improved histologic response in adult
311 patients with compensated liver disease who were treatment-naïve or had relapsed
312 following therapy with alpha interferon alone; pediatric patients previously untreated with
313 alpha interferon experienced a sustained virologic response. See REBETOL package
314 insert for additional information.

315

316 **Chronic Hepatitis B Adults** The safety and efficacy of INTRON A in the treatment of
317 chronic hepatitis B were evaluated in three clinical trials in which INTRON A doses of 30
318 to 35 million IU per week were administered subcutaneously (SC), as either 5 million IU
319 daily (QD), or 10 million IU three times a week (TIW) for 16 weeks vs no treatment. All
320 patients were 18 years of age or older with compensated liver disease, and had chronic
321 hepatitis B virus (HBV) infection (serum HBsAg positive for at least 6 months) and HBV
322 replication (serum HBeAg positive). Patients were also serum HBV-DNA positive, an
323 additional indicator of HBV replication, as measured by a research assay.^{7,8} All patients
324 had elevated serum alanine aminotransferase (ALT) and liver biopsy findings

325 compatible with the diagnosis of chronic hepatitis. Patients with the presence of
326 antibody to human immunodeficiency virus (anti-HIV) or antibody to hepatitis delta virus
327 (anti-HDV) in the serum were excluded from the studies.

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

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

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

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

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

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

356 Virologic response was associated with a reduction in serum ALT to normal or
357 near normal (less than or equal to 1.5 x the upper limit of normal) in 87% (13/15) of
358 patients responding to INTRON A therapy at 5 million IU QD, and 100% (23/23) of
359 patients responding to 10 million IU TIW.

360 Improvement in liver histology was evaluated in Studies 1 and 3 by comparison
361 of pretreatment and 6-month posttreatment liver biopsies using the semiquantitative
362 Knodell Histology Activity Index.⁹ No statistically significant difference in liver histology
363 was observed in treated patients compared to control patients in Study 1. Although
364 statistically significant histological improvement from baseline was observed in treated
365 patients in Study 3 ($P \leq 0.01$), there was no control group for comparison. Of those
366 patients exhibiting a virologic response following treatment with 5 million IU QD or 10
367 million IU TIW, histological improvement was observed in 85% (17/20) compared to
368 36% (9/25) of patients who were not virologic responders. The histological
369 improvement was due primarily to decreases in severity of necrosis, degeneration, and
370 inflammation in the periportal, lobular, and portal regions of the liver (Knodell Categories

371 I + II + III). Continued histological improvement was observed in four responding
 372 patients who lost serum HBsAg and were followed 2 to 4 years after the end of INTRON
 373 A therapy.¹⁰
 374

375 **Pediatrics** The safety and efficacy of INTRON A in the treatment of chronic hepatitis B
 376 was evaluated in one randomized controlled trial of 149 patients ranging from 1 year to
 377 17 years of age. Seventy-two patients were treated with 3 million IU/m² of INTRON A
 378 therapy administered subcutaneously three times a week (TIW) for 1 week; the dose
 379 was then escalated to 6 million IU/m² TIW for a minimum of 16 weeks up to 24 weeks.
 380 The maximum weekly dosage was 10 million IU TIW. Seventy-seven patients were
 381 untreated controls. Study entry and response criteria were identical to those described
 382 in the adult patient population.

383 Patients treated with INTRON A therapy had a better response (loss of HBV DNA
 384 and HBeAg at 24 weeks of follow-up) compared to the untreated controls (24% [17/72]
 385 vs 10% [8/77] *P*=0.05). Sixteen of the 17 responders treated with INTRON A therapy
 386 remained HBV DNA and HBeAg negative and had a normal serum ALT 12 to 24
 387 months after completion of treatment. Serum HBsAg became negative in 7 out of 17
 388 patients who responded to INTRON A therapy. None of the control patients who had an
 389 HBV DNA and HBeAg response became HBsAg negative. At 24 weeks of follow-up,
 390 normalization of serum ALT was similar in patients treated with INTRON A therapy
 391 (17%, 12/72) and in untreated control patients (16%, 12/77). Patients with a baseline
 392 HBV DNA less than 100 pg/mL were more likely to respond to INTRON A therapy than
 393 were patients with a baseline HBV DNA greater than 100 pg/mL (35% vs 9%,
 394 respectively). Patients who contracted hepatitis B through maternal vertical
 395 transmission had lower response rates than those who contracted the disease by other
 396 means (5% vs 31%, respectively). There was no evidence that the effects on HBV DNA
 397 and HBeAg were limited to specific subpopulations based on age, gender, or race.
 398
 399

TABLE 1
 RESPONSE BY BASELINE CD4 COUNT[†] IN AIDS-RELATED KS PATIENTS

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

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

400

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.

401
402

TABLE 3
VIROLOGIC RESPONSE[†] IN CHRONIC HEPATITIS B PATIENTS

Study Number	Treatment Group [†] - Number of Patients (%)						P [‡] Value
	INTRON A 5 million IU QD		INTRON A 10 million IU TIW		Untreated Controls		
1 ⁷	15/38	(39%)	--	--	3/42	(7%)	0.0009
2	--	--	10/24	(42%)	1/22	(5%)	0.005
3 ⁸	--	--	13/24 [§]	(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).

403

TABLE 4
ALT RESPONSES[†] IN CHRONIC HEPATITIS B PATIENTS

Study Number	Treatment Group - Number of Patients (%)						P [†] Value
	INTRON A 5 million IU QD		INTRON A 10 million IU TIW		Untreated Controls		
1	16/38	(42%)	--	--	8/42	(19%)	0.03
2	--	--	10/24	(42%)	1/22	(5%)	0.0034
3	--	--	12/24 [‡]	(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).

404

405 INDICATIONS AND USAGE

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

408

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

412

413 **Follicular Lymphoma** INTRON A is indicated for the initial treatment of clinically
414 aggressive (see **Clinical Pharmacology**) follicular Non-Hodgkin's Lymphoma in

415 conjunction with anthracycline-containing combination chemotherapy in patients 18
 416 years of age or older. Efficacy of INTRON A therapy in patients with low-grade, low-
 417 tumor burden follicular Non-Hodgkin's Lymphoma has not been demonstrated.

418

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

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

424

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

430

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

437

438 A liver biopsy should be performed to establish the diagnosis of chronic hepatitis.
 439 Patients should be tested for the presence of antibody to HCV. Patients with other
 440 causes of chronic hepatitis, including autoimmune hepatitis, should be excluded. Prior
 441 to initiation of INTRON A therapy, the physician should establish that the patient has
 442 compensated liver disease. The following patient entrance criteria for compensated liver
 443 disease were used in the clinical studies and should be considered before INTRON A
 444 treatment of patients with chronic hepatitis C:

445

- 445 • No history of hepatic encephalopathy, variceal bleeding, ascites, or other
 446 clinical signs of decompensation

447

- Bilirubin Less than or equal to 2 mg/dL

448

- Albumin Stable and within normal limits

449

- Prothrombin Time Less than 3 seconds prolonged

450

- WBC Greater than or equal to 3000/mm³

451

- Platelets Greater than or equal to 70,000/mm³

452

Serum creatinine should be normal or near normal.

453

454 Prior to initiation of INTRON A therapy, CBC and platelet counts should be
 455 evaluated in order to establish baselines for monitoring potential toxicity. These tests
 456 should be repeated at Weeks 1 and 2 following initiation of INTRON A therapy, and

457 monthly thereafter. Serum ALT should be evaluated at approximately 3-month intervals
 458 to assess response to treatment (see **DOSAGE AND ADMINISTRATION**).

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

464 INTRON A in combination with REBETOL® is indicated for the treatment of
 465 chronic hepatitis C in patients 3 years of age and older with compensated liver disease
 466 previously untreated with alpha interferon therapy and in patients 18 years of age and
 467 older who have relapsed following alpha interferon therapy. See REBETOL package
 468 insert for additional information.

469
 470 **Chronic Hepatitis B** INTRON A is indicated for the treatment of chronic hepatitis B in
 471 patients 1 year of age or older with compensated liver disease. Patients who have been
 472 serum HBsAg positive for at least 6 months and have evidence of HBV replication
 473 (serum HBeAg positive) with elevated serum ALT are candidates for treatment. Studies
 474 in these patients demonstrated that INTRON A therapy can produce virologic remission
 475 of this disease (loss of serum HBeAg) and normalization of serum aminotransferases.
 476 INTRON A therapy resulted in the loss of serum HBsAg in some responding patients.

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

- 483
- 484 • No history of hepatic encephalopathy, variceal bleeding, ascites, or other
 485 signs of clinical decompensation
 - 486 • Bilirubin Normal
 - 487 • Albumin Stable and within normal limits
 - 488 • Prothrombin Time *Adults* less than 3 seconds prolonged
 489 *Pediatrics* less than or equal to 2 seconds prolonged
 - 490 • WBC Greater than or equal to 4000/mm³
 - 491 • Platelets *Adults* greater than or equal to 100,000/mm³
 492 *Pediatrics* greater than or equal to 150,000/mm³
- 493

494 Patients with causes of chronic hepatitis other than chronic hepatitis B or chronic
 495 hepatitis C should not be treated with INTRON A. CBC and platelet counts should be
 496 evaluated prior to initiation of INTRON A therapy in order to establish baselines for
 497 monitoring potential toxicity. These tests should be repeated at treatment Weeks 1, 2,
 498 4, 8, 12, and 16. Liver function tests, including serum ALT, albumin, and bilirubin,
 499 should be evaluated at treatment Weeks 1, 2, 4, 8, 12, and 16. HBeAg, HBsAg, and

500 ALT should be evaluated at the end of therapy, as well as 3- and 6-months posttherapy,
 501 since patients may become virologic responders during the 6-month period following the
 502 end of treatment. In clinical studies in adults, 39% (15/38) of responding patients lost
 503 HBeAg 1 to 6 months following the end of INTRON A therapy. Of responding patients
 504 who lost HBsAg, 58% (7/12) did so 1 to 6 months posttreatment.

505 A transient increase in ALT greater than or equal to 2 times baseline value (flare)
 506 can occur during INTRON A therapy for chronic hepatitis B. In clinical trials in adults
 507 and pediatrics, this flare generally occurred 8 to 12 weeks after initiation of therapy and
 508 was more frequent in responders (*adults* 63%, 24/38; *pediatrics* 59%, 10/17) than in
 509 nonresponders (*adults* 27%, 13/48; *pediatrics* 35%, 19/55). However, in adults and
 510 pediatrics, elevations in bilirubin greater than or equal to 3 mg/dL (greater than or equal
 511 to 2 times ULN) occurred infrequently (*adults* 2%, 2/86; *pediatrics* 3%, 2/72) during
 512 therapy. When ALT flare occurs, in general, INTRON A therapy should be continued
 513 unless signs and symptoms of liver failure are observed. During ALT flare, clinical
 514 symptomatology and liver function tests including ALT, prothrombin time, alkaline
 515 phosphatase, albumin, and bilirubin, should be monitored at approximately 2-week
 516 intervals (see **WARNINGS**).

517

518 **CONTRAINDICATIONS**

519 INTRON® A is contraindicated in patients with:

- 520 • Hypersensitivity to interferon alpha or any component of the product
- 521 • Autoimmune hepatitis
- 522 • Decompensated liver disease.

523

524 INTRON A and REBETOL® combination therapy is additionally contraindicated in:

- 525 • Patients with hypersensitivity to ribavirin or any other component of the product
- 526 • Women who are pregnant
- 527 • Men whose female partners are pregnant
- 528 • Patients with hemoglobinopathies (e.g., thalassemia major, sickle cell anemia)
- 529 • Patients with creatinine clearance less than 50 mL/min.

530 See REBETOL package insert for additional information.

531

532 **WARNINGS**

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

541

542 **Cardiovascular Disorders**

543 INTRON A therapy should be used cautiously in patients with a history of cardiovascular
 544 disease. Those patients with a history of myocardial infarction and/or previous or
 545 current arrhythmic disorder who require INTRON A therapy should be closely monitored

546 (see **PRECAUTIONS, Laboratory Tests**). Cardiovascular adverse experiences, which
547 include hypotension, arrhythmia, or tachycardia of 150 beats per minute or greater, and
548 rarely, cardiomyopathy and myocardial infarction have been observed in some INTRON
549 A-treated patients. Some patients with these adverse events had no history of
550 cardiovascular disease. Transient cardiomyopathy was reported in approximately 2% of
551 the AIDS-Related Kaposi's Sarcoma patients treated with INTRON A. Hypotension may
552 occur during INTRON A administration, or up to 2 days posttherapy, and may require
553 supportive therapy including fluid replacement to maintain intravascular volume.

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

558

559 **Cerebrovascular Disorders**

560 Ischemic and hemorrhagic cerebrovascular events have been observed in patients
561 treated with interferon alpha-based therapies, including INTRON A. Events occurred in
562 patients with few or no reported risk factors for stroke, including patients less than 45
563 years of age. Because these are spontaneous reports, estimates of frequency cannot
564 be made and a causal relationship between interferon alpha-based therapies and these
565 events is difficult to establish.

566

567 **Neuropsychiatric Disorders**

568 DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL IDEATION,
569 SUICIDAL ATTEMPTS, AND COMPLETED SUICIDES, HOMICIDAL IDEATION, AND
570 AGGRESSIVE BEHAVIOR SOMETIMES DIRECTED TOWARDS OTHERS, HAVE
571 BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALPHA
572 INTERFERONS, INCLUDING INTRON A THERAPY. If patients develop psychiatric
573 problems, including clinical depression, it is recommended that the patients be carefully
574 monitored during treatment and in the 6-month follow-up period.

575 INTRON A should be used with caution in patients with a history of psychiatric
576 disorders. INTRON A therapy should be discontinued for any patient developing severe
577 psychiatric disorder during treatment. Obtundation and coma have also been observed
578 in some patients, usually elderly, treated at higher doses. While these effects are
579 usually rapidly reversible upon discontinuation of therapy, full resolution of symptoms
580 has taken up to 3 weeks in a few severe episodes. If psychiatric symptoms persist or
581 worsen, or suicidal ideation or aggressive behavior towards others is identified, it is
582 recommended that treatment with INTRON A be discontinued and the patient followed,
583 with psychiatric intervention as appropriate. Narcotics, hypnotics, or sedatives may be
584 used concurrently with caution and patients should be closely monitored until the
585 adverse effects have resolved. Suicidal ideation or attempts occurred more frequently
586 among pediatric patients, primarily adolescents, compared to adult patients (2.4% vs
587 1%) during treatment and off-therapy follow-up. Cases of encephalopathy have also
588 been observed in some patients, usually elderly, treated with higher doses of INTRON
589 A.

590 Treatment with interferons may be associated with exacerbated symptoms of
591 psychiatric disorders in patients with co-occurring psychiatric and substance use

592 disorders. If treatment with interferons is initiated in patients with prior history or
593 existence of psychiatric condition or with a history of substance use disorders, treatment
594 considerations should include the need for drug screening and periodic health
595 evaluation, including psychiatric symptom monitoring. Early intervention for re-
596 emergence or development of neuropsychiatric symptoms and substance use is
597 recommended.

598

599 **Bone Marrow Toxicity**

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

606

607 **Ophthalmologic Disorders**

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

617

618 **Endocrine Disorders**

619 Infrequently, patients receiving INTRON A therapy developed thyroid
620 abnormalities, either hypothyroid or hyperthyroid. The mechanism by which INTRON A
621 may alter thyroid status is unknown. Patients with preexisting thyroid abnormalities
622 whose thyroid function cannot be maintained in the normal range by medication should
623 not be treated with INTRON A. Prior to initiation of INTRON A therapy, serum TSH
624 should be evaluated. Patients developing symptoms consistent with possible thyroid
625 dysfunction during the course of INTRON A therapy should have their thyroid function
626 evaluated and appropriate treatment instituted. Therapy should be discontinued for
627 patients developing thyroid abnormalities during treatment whose thyroid function
628 cannot be normalized by medication. Discontinuation of INTRON A therapy has not
629 always reversed thyroid dysfunction occurring during treatment. Diabetes mellitus has
630 been observed in patients treated with alpha interferons. Patients with these conditions
631 who cannot be effectively treated by medication should not begin INTRON A therapy.
632 Patients who develop these conditions during treatment and cannot be controlled with
633 medication should not continue INTRON A therapy.

634

635 **Gastrointestinal Disorders**

636 Hepatotoxicity, including fatality, has been observed in interferon alpha-treated
637 patients, including those treated with INTRON A. Any patient developing liver function

638 abnormalities during treatment should be monitored closely and if appropriate,
639 treatment should be discontinued.

640

641 **Pulmonary Disorders**

642 Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial
643 pneumonitis, pulmonary hypertension, and sarcoidosis, some resulting in respiratory
644 failure and/or patient deaths, may be induced or aggravated by INTRON A or other
645 alpha interferons. Recurrence of respiratory failure has been observed with interferon
646 rechallenge. The etiologic explanation for these pulmonary findings has yet to be
647 established. Any patient developing fever, cough, dyspnea, or other respiratory
648 symptoms should have a chest X-ray taken. If the chest X-ray shows pulmonary
649 infiltrates or there is evidence of pulmonary function impairment, the patient should be
650 closely monitored, and, if appropriate, interferon alpha treatment should be
651 discontinued. While this has been reported more often in patients with chronic hepatitis
652 C treated with interferon alpha, it has also been reported in patients with oncologic
653 diseases treated with interferon alpha.

654

655 **Autoimmune Disorders**

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

663

664 **Human Albumin**

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

670

671 **AIDS-Related Kaposi's Sarcoma** INTRON A therapy should not be used for patients
672 with rapidly progressive visceral disease (see **CLINICAL PHARMACOLOGY**). Also of
673 note, there may be synergistic adverse effects between INTRON A and zidovudine.
674 Patients receiving concomitant zidovudine have had a higher incidence of neutropenia
675 than that expected with zidovudine alone. Careful monitoring of the WBC count is
676 indicated in all patients who are myelosuppressed and in all patients receiving other
677 myelosuppressive medications. The effects of INTRON A when combined with other
678 drugs used in the treatment of AIDS-related disease are unknown.

679

680 **Chronic Hepatitis C and Chronic Hepatitis B** Patients with decompensated liver
681 disease, autoimmune hepatitis or a history of autoimmune disease, and patients who
682 are immunosuppressed transplant recipients should not be treated with INTRON A.
683 There are reports of worsening liver disease, including jaundice, hepatic

684 encephalopathy, hepatic failure, and death following INTRON A therapy in such
685 patients. Therapy should be discontinued for any patient developing signs and
686 symptoms of liver failure.

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

697

698 **Peripheral Neuropathy**

699 Peripheral neuropathy has been reported when alpha interferons were given in
700 combination with telbivudine. In one clinical trial, an increased risk and severity of
701 peripheral neuropathy was observed with the combination use of telbivudine and
702 pegylated interferon alfa-2a as compared to telbivudine alone. The safety and efficacy
703 of telbivudine in combination with interferons for the treatment of chronic hepatitis B has
704 not been demonstrated.

705

706 **Use with Ribavirin (See also REBETOL package insert)** REBETOL may cause birth
707 defects and/or death of the unborn child. REBETOL therapy should not be started until
708 a report of a negative pregnancy test has been obtained immediately prior to planned
709 initiation of therapy. Patients should use at least two forms of contraception and have
710 monthly pregnancy tests (see **CONTRAINDICATIONS** and **PRECAUTIONS:**
711 Information for Patients).

712

713 Combination treatment with INTRON A and REBETOL was associated with
714 hemolytic anemia. Hemoglobin less than 10 g/dL was observed in approximately 10%
715 of adult and pediatric patients in clinical trials. Anemia occurred within 1 to 2 weeks of
716 initiation of ribavirin therapy. Combination treatment with INTRON A and REBETOL
717 should **not** be used in patients with creatinine clearance less than 50 mL/min. See
718 REBETOL package insert for additional information.

719

720 **PRECAUTIONS**

721 **General** Acute serious hypersensitivity reactions (e.g., urticaria, angioedema,
722 bronchoconstriction, anaphylaxis) have been observed rarely in INTRON® A-treated
723 patients; if such an acute reaction develops, the drug should be discontinued
724 immediately and appropriate medical therapy instituted. Transient rashes have
725 occurred in some patients following injection, but have not necessitated treatment
726 interruption.

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

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

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

736

737 **Triglycerides** Elevated triglyceride levels have been observed in patients treated with
738 interferons, including INTRON A therapy. Elevated triglyceride levels should be
739 managed as clinically appropriate. Hypertriglyceridemia may result in pancreatitis.
740 Discontinuation of INTRON A therapy should be considered for patients with
741 persistently elevated triglycerides (e.g., triglycerides greater than 1000 mg/dL)
742 associated with symptoms of potential pancreatitis, such as abdominal pain, nausea, or
743 vomiting.

744

745 **Drug Interactions** Interactions between INTRON A and other drugs have not been
746 fully evaluated. Caution should be exercised when administering INTRON A therapy in
747 combination with other potentially myelosuppressive agents such as zidovudine.
748 Concomitant use of alpha interferon and theophylline decreases theophylline clearance,
749 resulting in a 100% increase in serum theophylline levels.

750

751 **Information for Patients** Patients receiving INTRON A alone or in combination with
752 REBETOL® should be informed of the risks and benefits associated with treatment and
753 should be instructed on proper use of the product. To supplement your discussion with
754 a patient, you may wish to provide patients with a copy of the **MEDICATION GUIDE**.

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

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

768

769 If a decision is made to allow a patient to self-administer INTRON A, they should
770 be instructed, based on their treatment, if they should inject a dose of INTRON® A
771 subcutaneously or intramuscularly. If it is too difficult for them to inject themselves, they
772 should be instructed to ask someone who has been trained to give the injection to them.
773 Patients should be instructed on the importance of site selection for self-administering
774 the injection, as well as the importance on rotating the injection sites. A puncture

775 resistant container for the disposal of needles and syringes should be supplied.
776 Patients self-administering INTRON A should be instructed on the proper disposal of
777 needles and syringes and cautioned against reuse.

778

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

786

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

790

- 791 • Standard hematologic tests - including hemoglobin, complete and differential
792 white blood cell counts, and platelet count.
- 793 • Blood chemistries - electrolytes, liver function tests, and TSH.

794

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

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

802 Baseline chest X-rays are suggested and should be repeated if clinically
803 indicated.

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

807 For specific recommendations in chronic hepatitis C and chronic hepatitis B, see

808 **INDICATIONS AND USAGE.**

809

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

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

818 Mutagenicity studies have demonstrated that INTRON A is not mutagenic.

819 Studies in mice (0.1, 1.0 million IU/day), rats (4, 20, 100 million IU/kg/day), and
820 cynomolgus monkeys (1.1 million IU/kg/day; 0.25, 0.75, 2.5 million IU/kg/day) injected

821 with INTRON A for up to 9 days, 3 months, and 1 month, respectively, have revealed no
822 evidence of toxicity. However, in cynomolgus monkeys (4, 20, 100 million IU/kg/day)
823 injected daily for 3 months with INTRON A, toxicity was observed at the mid and high
824 doses and mortality was observed at the high dose.

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

827 INTRON A in combination with REBETOL should be used with caution in fertile
828 men. See the REBETOL package insert for additional information.

829

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

836

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

843

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

849

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

855

856 **Pediatric Use**

857 **General** Safety and effectiveness in pediatric patients have not been established for
858 indications other than chronic hepatitis B and chronic hepatitis C.

859 **Chronic Hepatitis B** Safety and effectiveness in pediatric patients ranging in age from
860 1 to 17 years have been established based upon one controlled clinical trial (see
861 **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and DOSAGE AND**
862 **ADMINISTRATION, Chronic Hepatitis B Pediatrics**).

863 **Chronic Hepatitis C** Safety and effectiveness in pediatric patients ranging in age from
864 3 to 16 years have been established based upon clinical studies in 118 patients. See
865 REBETOL package insert for additional information. Suicidal ideation or attempts
866 occurred more frequently among pediatric patients compared to adult patients (2.4% vs

1%) during treatment and off-therapy follow-up (see **WARNINGS, Neuropsychiatric Disorders**). During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 7%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 9%). A general reversal of these trends was noted during the 24-week post-treatment period.

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

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

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

ADVERSE REACTIONS

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

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

TREATMENT-RELATED ADVERSE EXPERIENCES BY INDICATION

ADVERSE EXPERIENCE	Dosing Regimens Percentage (%) of Patients*									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C ¹	CHRONIC HEPATITIS B		
					Adults	Pediatrics		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

TREATMENT-RELATED ADVERSE EXPERIENCES BY INDICATION

	Dosing Regimens									
	Percentage (%) of Patients ^a									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS- RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C ^b	CHRONIC HEPATITIS B		
							Adults	Pediatrics		
	20 MIU/m ²									
Induction (IV)	5 MIU	2 MIU/m ²	1	30	35	3	5	10	6	
10 MIU/m ²	TIW/SC	TIW/SC	MIU/lesion	MIU/m ²	MIU	MIU	MIU	MIU	MIU/m ²	
Maintenance (SC)				TIW/S C	QD/S C	TIW	QD	TIW	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 ^a									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSII'S SARCOMA		CHRONIC HEPATITIS C ^b	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

	Dosing Regimens									
	Percentage (%) of Patients [*]									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS- RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C [†]	CHRONIC HEPATITIS B		
							Adults	Pediatrics		
	20 MIU/m ²									
	Induction (IV)	5 MIU	2 MIU/m ²	1	30	35	3	5	10	6
	10 MIU/m ²	TIW/SC	TIW/SC	MIU/lesion	MIU/m ²	MIU	MIU	MIU	MIU	MIU/m ²
	Maintenance (SC)				TIW/S C	QD/S C	TIW	QD	TIW	TIW
ADVERSE EXPERIENCE	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% in 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

901 **Hairy Cell Leukemia** The adverse reactions most frequently reported during clinical
902 trials in 145 patients with hairy cell leukemia were the “flu-like” symptoms of fever
903 (68%), fatigue (61%), and chills (46%).
904

905 **Malignant Melanoma** The INTRON A dose was modified because of adverse
906 events in 65% (n=93) of the patients. INTRON A therapy was discontinued because
907 of adverse events in 8% of the patients during induction and 18% of the patients
908 during maintenance. The most frequently reported adverse reaction was fatigue,
909 which was observed in 96% of patients. Other adverse reactions that were recorded
910 in greater than 20% of INTRON A-treated patients included neutropenia (92%), fever
911 (81%), myalgia (75%), anorexia (69%), vomiting/nausea (66%), increased SGOT
912 (63%), headache (62%), chills (54%), depression (40%), diarrhea (35%), alopecia
913 (29%), altered taste sensation (24%), dizziness/vertigo (23%), and anemia (22%).

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

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

937 Twenty-eight percent of CHVP plus INTRON A-treated patients had a
938 temporary modification/interruption of their INTRON A therapy, but only 13 patients
939 (10%) permanently stopped INTRON A therapy because of toxicity. There were
940 four deaths on study; two patients committed suicide in the CHVP plus INTRON A
941 arm and two patients in the CHVP arm had unwitnessed sudden death. Three
942 patients with hepatitis B (one of whom also had alcoholic cirrhosis) developed
943 hepatotoxicity leading to discontinuation of INTRON A. Other reasons for
944 discontinuation included intolerable asthenia (5/135), severe flu symptoms (2/135),
945 and one patient each with exacerbation of ankylosing spondylitis, psychosis, and
946 decreased ejection fraction.

947

948 **Condylomata Acuminata** Eighty-eight percent (311/352) of patients treated with
949 INTRON A for condylomata acuminata who were evaluable for safety reported an
950 adverse reaction during treatment. The incidence of the adverse reactions reported
951 increased when the number of treated lesions increased from one to five. All 40
952 patients who had five warts treated reported some type of adverse reaction during
953 treatment.

954

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

957

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

962

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

974

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

984

Of the patients achieving a complete response after 6 months of therapy,
985 12/79 (15%) subsequently discontinued INTRON A treatment during extended
986 therapy because of adverse events, and 23/79 (29%) experienced severe adverse
987 events (WHO grade 3 or 4) during extended therapy.

988

In patients using combination treatment with INTRON A and REBETOL, the
989 primary toxicity observed was hemolytic anemia. Reductions in hemoglobin levels
990 occurred within the first 1 to 2 weeks of therapy. Cardiac and pulmonary events
991 associated with anemia occurred in approximately 10% of patients treated with

992 INTRON A/REBETOL therapy. See REBETOL package insert for additional
993 information.

994

995 **Chronic Hepatitis B**

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

1000 Adverse reactions classified as severe (causing a significant interference with
1001 normal daily activities or clinical state) were reported in 21% to 44% of patients. The
1002 severe adverse reactions reported most frequently were the “flu-like” symptoms of
1003 fever (28%), fatigue (15%), headache (5%), myalgia (4%), rigors (4%), and other
1004 severe “flu-like” symptoms, which occurred in 1% to 3% of patients. Other severe
1005 adverse reactions occurring in more than one patient were alopecia (8%), anorexia
1006 (6%), depression (3%), nausea (3%), and vomiting (2%).

1007 To manage side effects, the dose was reduced, or INTRON A therapy was
1008 interrupted in 25% to 38% of patients. Five percent of patients discontinued
1009 treatment due to adverse experiences.

1010

1011 **Pediatrics** In pediatric patients, the most frequently reported adverse events were
1012 those commonly associated with interferon treatment: flu-like symptoms (100%),
1013 gastrointestinal system disorders (46%), and nausea and vomiting (40%).
1014 Neutropenia (13%) and thrombocytopenia (3%) were also reported. None of the
1015 adverse events were life threatening. The majority were moderate to severe and
1016 resolved upon dose reduction or drug discontinuation.

1017

1018

ABNORMAL LABORATORY TEST VALUES BY INDICATION

	Dosing Regimens Percentage (%) of Patients									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSI'S SARCOMA	CHRONIC HEPATITIS C	CHRONIC HEPATITIS B			
							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/SC	35 MIU QD/SC	3 MIU TIW	5 MIU QD	10 MIU TIW	6 MIU/m ² TIW
Laboratory Tests	N=143	N=135	N=145	N=352	N=69-73	N=26-28	N=140-171	N=96-101	N=75-103	N=113-115
Hemoglobin	22	8	NA	--	1	15	26 [†]	32 [†]	23 [†]	17 ^{**}
White Blood Cell Count	"	--	NA	17	10	22	26 [†]	68 [†]	34 [†]	9 [†]
Platelet Count	15	13	NA	--	0	8	15 [‡]	12 [‡]	5 [‡]	1 [‡]
Serum Creatinine	3	2	0	--	--	--	6	3	0	3
Alkaline Phosphatase	13	--	4	--	--	--	--	8	4	0
Lactate Dehydrogenase	1	--	0	--	--	--	--	--	--	--
Serum Urea Nitrogen	12	4	0	--	--	--	--	2	0	2
SGOT	63	24	4	12	11	41	--	--	--	--
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

1019 Postmarketing Experience

1020

1021

1022 The following adverse reactions have been identified during post-approval use of
1023 INTRON A alone or in combination with REBETOL. Because these reactions are
1024 reported voluntarily from a population of uncertain size, it is not always possible to
1025 reliably estimate their frequency or establish a causal relationship to drug exposure.

1026

1027 *Blood and Lymphatic System Disorders*

1028 pancytopenia (concurrent anemia, leukopenia, thrombocytopenia), aplastic anemia,

1029 pure red cell aplasia, thrombotic thrombocytopenic purpura, idiopathic

1030 thrombocytopenic purpura

1031 *Ear and Labyrinth Disorders*

1032 hearing loss

1033 *Endocrine Disorders*

1034 hypopituitarism

1035 *Eye Disorders*

1036 Vogt-Koyanagi-Harada syndrome, serous retinal detachment

1037 *Gastrointestinal Disorders*

1038 pancreatitis

1039 *General Disorders and Administration Site Conditions*

1040 asthenic conditions (including asthenia, malaise, fatigue)

1041 *Immune System Disorders*

1042 cases of acute hypersensitivity reactions, including anaphylaxis and angioedema,

1043 systemic lupus erythematosus, sarcoidosis or exacerbation of sarcoidosis

1044 *Musculoskeletal and Connective Tissue Disorders*

1045 myositis

1046 *Nervous System Disorders*

1047 peripheral neuropathy

1048 *Psychiatric Disorders*

1049 homicidal ideation, psychosis including hallucinations

1050 *Renal and Urinary Disorders*

1051 renal failure, renal insufficiency, nephrotic syndrome

1052 *Respiratory, Thoracic and Mediastinal Disorders*

1053 pulmonary hypertension

1054 *Skin and Subcutaneous Tissue Disorders*

1055 injection site necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis,

1056 erythema multiforme, urticaria

1057

1058

1059 OVERDOSAGE

1060 There is limited experience with overdose. Postmarketing surveillance includes

1061 reports of patients receiving a single dose as great as 10 times the recommended

1062 dose. In general, the primary effects of an overdose are consistent with the effects

1063 seen with therapeutic doses of interferon alfa-2b. Hepatic enzyme abnormalities,

1064 renal failure, hemorrhage, and myocardial infarction have been reported with single

1065 administration overdoses and/or with longer durations of treatment than prescribed
 1066 (see **ADVERSE REACTIONS**). Toxic effects after ingestion of interferon alfa-2b are
 1067 not expected because interferons are poorly absorbed orally. Consultation with a
 1068 poison center is recommended.

1069
 1070 **Treatment** There is no specific antidote for interferon alfa-2b. Hemodialysis and
 1071 peritoneal dialysis are not considered effective for treatment of overdose.

1072 1073 **DOSAGE AND ADMINISTRATION**

1074 1075 **General**

1076
 1077 **IMPORTANT: INTRON® A** is supplied as 1) Powder for Injection/Reconstitution; 2)
 1078 Solution for Injection in Vials; 3) Solution for Injection in Multidose Pens. **Not all**
 1079 **dosage forms and strengths are appropriate for some indications.** It is
 1080 important that you carefully read the instructions below for the indication you are
 1081 treating to ensure you are using an appropriate dosage form and strength.

1082
 1083 To enhance the tolerability of INTRON A, injections should be administered in the
 1084 evening when possible.

1085
 1086 To reduce the incidence of certain adverse reactions, acetaminophen may be
 1087 administered at the time of injection.

1088
 1089 The solution should be allowed to come to room temperature before using.

1090 1091 **Hairy Cell Leukemia (see DOSAGE AND ADMINISTRATION, General)**

1092
 1093 **Dose:** The recommended dose for the treatment of hairy cell leukemia is 2 million
 1094 IU/m² administered intramuscularly or subcutaneously 3 times a week for up to 6
 1095 months. Patients with platelet counts of less than 50,000/mm³ should not be
 1096 administered INTRON A intramuscularly, but instead by subcutaneous
 1097 administration. Patients who are responding to therapy may benefit from continued
 1098 treatment.

1099 1100	Dosage Forms for this Indication			Fixed Doses
	Dosage Form	Concentration	Route	
	Powder 10 MIU (single-dose)	10 MIU/mL	IM, 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

1101
 1102 **NOTE: INTRON A Powder for Injection does not contain a preservative. The**
 1103 **vial must be discarded after reconstitution and withdrawal of a single dose.**

1104 1105 **Dose Adjustment:**

1106

- 1107 • If severe adverse reactions develop, the dosage should be modified (50%
- 1108 reduction) or therapy should be temporarily withheld until the adverse
- 1109 reactions abate and then resume at 50% (1 MIU/m² TIW).
- 1110 • If severe adverse reactions persist or recur following dosage adjustment,
- 1111 INTRON A should be permanently discontinued.
- 1112 • INTRON A should be discontinued for progressive disease or failure to
- 1113 respond after six months of treatment.

1114

1115 **Malignant Melanoma (see DOSAGE AND ADMINISTRATION, General)**

1116

1117 INTRON A adjuvant treatment of malignant melanoma is given in two phases,

1118 induction and maintenance.

1119

1120 **Induction Recommended Dose:**

1121

1122 The recommended daily dose of INTRON A in induction is 20 million IU/m² as an

1123 intravenous infusion, over 20 minutes, 5 consecutive days per week, for 4 weeks

1124 (see Dose Adjustment below).

1125

1126

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

1127

1128 **NOTE: INTRON A Solution for Injection in vials or Multidose Pens is NOT**

1129 **recommended for intravenous administration and should not be used for the**

1130 **induction phase of malignant melanoma.**

1131

1132 **NOTE: INTRON A Powder for Injection does not contain a preservative. The**

1133 **vial must be discarded after reconstitution and withdrawal of a single dose.**

1134

1135 **Dose Adjustment:**

1136

1137 **NOTE:** Regular laboratory testing should be performed to monitor laboratory

1138 abnormalities for the purpose of dose modifications (see **PRECAUTIONS,**

1139 **Laboratory Tests**).

1140

- 1141 • INTRON A should be withheld for severe adverse reactions, including
- 1142 granulocyte counts greater than 250/mm³ but less than 500/mm³ or
- 1143 SGPT/SGOT greater than 5-10x upper limit of normal, until adverse reactions
- 1144 abate. INTRON A treatment should be restarted at 50% of the previous dose.
- 1145 • INTRON A should be permanently discontinued for:
 - 1146 ○ Toxicity that does not abate after withholding INTRON A
 - 1147 ○ Severe adverse reactions which recur in patients receiving reduced
 - 1148 doses of INTRON A

- 1149 ○ Granulocyte count less than 250/mm³ or SGPT/SGOT of greater than
- 1150 10x upper limit of normal

1151

1152 **Maintenance Recommended Dose:**

1153

1154 The recommended dose of INTRON A for maintenance is 10 million IU/m² as a
 1155 subcutaneous injection three times per week for 48 weeks (see Dose Adjustment
 1156 below).

1157

1158

Dosage Form	Dosage Forms for this Indication			Fixed Doses
	Concentration	Route		
Powder 10 MIU (single-dose)*	10 MIU/mL	SC		N/A
Powder 18 MIU (single dose)**	18 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

1159

*Patients receiving 50% dose reduction only

1160

**Patients receiving full dose only

1161

1162 **NOTE: INTRON A Powder for Injection does not contain a preservative. The**
 1163 **vial must be discarded after reconstitution and withdrawal of a single dose.**

1164

Dose Adjustment:

1165

1166 **NOTE:** Regular laboratory testing should be performed to monitor laboratory
 1167 abnormalities for the purpose of dose modifications (see **PRECAUTIONS,**
 1168 **Laboratory Tests**).

1169

- 1170 • INTRON A should be withheld for severe adverse reactions, including
- 1171 granulocyte counts greater than 250/mm³ but less than 500/mm³ or
- 1172 SGPT/SGOT greater than 5-10x upper limit of normal, until adverse reactions
- 1173 abate. INTRON A treatment should be restarted at 50% of the previous dose.

1174

- 1175 • INTRON A should be permanently discontinued for:
 - 1176 ○ Toxicity that does not abate after withholding INTRON A
 - 1177 ○ Severe adverse reactions which recur in patients receiving reduced
 - 1178 doses of INTRON A
 - 1179 ○ Granulocyte count less than 250/mm³ or SGPT/SGOT of greater than
 - 1180 10x upper limit of normal

1181

1182 **Follicular Lymphoma (see DOSAGE AND ADMINISTRATION, General)**

1183

1184 **Dose:** The recommended dose of INTRON A for the treatment of follicular
 1185 lymphoma is 5 million IU subcutaneously three times per week for up to 18 months
 1186 in conjunction with anthracycline-containing chemotherapy regimen and following
 1187 completion of the chemotherapy regimen.

1188

1189

Dosage Forms for this Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 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

1190

1191

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

1192

1193

1194

Dose Adjustment:

1195

1196

- Doses of myelosuppressive drugs were reduced by 25% from a full-dose CHOP regimen, and cycle length increased by 33% (e.g., from 21 to 28 days) when alpha interferon was added to the regimen.

1197

1198

1199

- Delay chemotherapy cycle if neutrophil count was less than 1500/mm³ or platelet count was less than 75,000/mm³.

1200

1201

- INTRON A should be permanently discontinued if SGOT exceeds greater than 5x the upper limit of normal or serum creatinine greater than 2.0 mg/dL (see **WARNINGS**).

1202

1203

1204

- Administration of INTRON A therapy should be withheld for a neutrophil count less than 1000/mm³, or a platelet count less than 50,000/mm³.

1205

1206

- INTRON A dose should be reduced by 50% (2.5 MIU TIW) for a neutrophil count greater than 1000/mm³, but less than 1500/mm³. The INTRON A dose may be re-escalated to the starting dose (5 million IU TIW) after resolution of hematologic toxicity (ANC greater than 1500/mm³).

1207

1208

1209

1210

1211

Condylomata Acuminata (see DOSAGE AND ADMINISTRATION, General)

1212

1213

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

1214

1215

1216

1217

Dosage Forms for this Indication

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

1218

1219

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

1220

1221

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

1222

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

1223

1224

1225

1226

Dose Adjustment: None

1227

1228

1229 **Technique for Injection:**

1230 The injection should be administered intralesionally using a Tuberculin or similar
 1231 syringe and a 25-to 30-gauge needle. The needle should be directed at the center
 1232 of the base of the wart and at an angle almost parallel to the plane of the skin
 1233 (approximately that in the commonly used PPD test). This will deliver the interferon
 1234 to the dermal core of the lesion, infiltrating the lesion and causing a small wheal.
 1235 Care should be taken not to go beneath the lesion too deeply; subcutaneous
 1236 injection should be avoided, since this area is below the base of the lesion. Do not
 1237 inject too superficially since this will result in possible leakage, infiltrating only the
 1238 keratinized layer and not the dermal core.

1239
 1240 **AIDS-Related Kaposi's Sarcoma (see DOSAGE AND ADMINISTRATION,**
 1241 **General)**

1242
 1243 **Dose:** The recommended dose of INTRON A for Kaposi's Sarcoma is 30 million
 1244 IU/m²/dose administered subcutaneously or intramuscularly three times a week until
 1245 disease progression or maximal response has been achieved after 16 weeks of
 1246 treatment. Dose reduction is frequently required (see **Dose Adjustment** below).
 1247
 1248

Dosage Form	Dosage Forms for this Indication	
	Concentration	Route
Powder 50 MIU	50 MIU/mL	IM, SC

1249

1250 **NOTE: INTRON A Solution for Injection either in vials or in Multidose Pens**
 1251 **should NOT be used for AIDS-Related Kaposi's Sarcoma.**

1252

1253 **NOTE: INTRON A Powder for Injection does not contain a preservative. The**
 1254 **vial must be discarded after reconstitution and withdrawal of a single dose.**

1255

1256 **Dose Adjustment:**

1257

- 1258 • INTRON A dose should be reduced by 50% or withheld for severe adverse
 1259 reactions.
- 1260 • INTRON A may be resumed at a reduced dose if severe adverse reactions
 1261 abate with interruption of dosing.
- 1262 • INTRON A should be permanently discontinued if severe adverse reactions
 1263 persist or if they recur in patients receiving a reduced dose.

1264

1265 **Chronic Hepatitis C (see DOSAGE AND ADMINISTRATION, General)**

1266

1267 **Dose:** The recommended dose of INTRON A for the treatment of chronic hepatitis C
 1268 is 3 million IU three times a week (TIW) administered subcutaneously or
 1269 intramuscularly. In patients tolerating therapy with normalization of ALT at 16 weeks
 1270 of treatment, INTRON A therapy should be extended to 18 to 24 months (72 to 96
 1271 weeks) at 3 million IU TIW to improve the sustained response rate (see **CLINICAL**
 1272 **PHARMACOLOGY, Chronic Hepatitis C**). Patients who do not normalize their

1273 ALTs or have persistently high levels of HCV RNA after 16 weeks of therapy rarely
 1274 achieve a sustained response with extension of treatment. Consideration should be
 1275 given to discontinuing these patients from therapy.

1276 When INTRON A is administered in combination with REBETOL®, patients
 1277 with impaired renal function and/or those over the age of 50 should be carefully
 1278 monitored with respect to the development of anemia. See REBETOL package
 1279 insert for dosing when used in combination with REBETOL for adults and pediatric
 1280 patients.

1281
 1282
 1283

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

1284
 1285

1286 **Dose adjustment:** If severe adverse reactions develop during INTRON A treatment,
 1287 the dose should be modified (50% reduction) or therapy should be temporarily
 1288 discontinued until the adverse reactions abate. If intolerance persists after dose
 1289 adjustment, INTRON A therapy should be discontinued.

1290
 1291
 1292

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

1293 **Dose:** The recommended dose of INTRON A for the treatment of chronic hepatitis B
 1294 is 30 to 35 million IU per week, administered subcutaneously or intramuscularly,
 1295 either as 5 million IU daily (QD) or as 10 million IU three times a week (TIW) for 16
 1296 weeks.

1297
 1298

Dosage Form	Dosage Forms for this Indication		Fixed Doses
	Concentration	Route	
Powder 10 MIU (single-dose)	10 MIU/mL	IM, 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

1299

1300 **NOTE: INTRON A Powder for Injection does not contain a preservative. The**
 1301 **vial must be discarded after reconstitution and withdrawal of a single dose.**

1302

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

1303

1304 **Dose:** The recommended dose of INTRON A for the treatment of chronic hepatitis B
 1305 is 3 million IU/m² three times a week (TIW) for the first week of therapy followed by
 1306 dose escalation to 6 million IU/m² TIW (maximum of 10 million IU TIW) administered
 1307 subcutaneously for a total duration of 16 to 24 weeks.

1308
 1309
 1310

Dosage Form	Dosage Forms for this Indication		Fixed Doses
	Concentration	Route	
Powder 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

1311

1312

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

1313

1314

1315

1316

1317

1318

1319

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.

1320

1321

1322

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

<u>INTRON A Dose</u>	<u>White Blood Cell Count</u>	<u>Granulocyte Count</u>	<u>Platelet Count</u>
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

1323

1324

1325

1326

1327

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.

1328

PREPARATION AND ADMINISTRATION

1329

1330

1331

Reconstitution of INTRON® A Powder for Injection

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1333

1334

1335

1336

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1338

1339

1340

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

1341

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

1342

1343

1344

1345

1346

1347

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

1348

1349

1350

1351

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

1352 Parenteral drug products should be inspected visually for particulate matter and
1353 discoloration prior to administration.

1354

1355 • **Intravenous Infusion**

1356 The infusion solution should be prepared immediately prior to use. Based on the
1357 desired dose, the appropriate vial strength(s) of INTRON A should be reconstituted
1358 with the diluent provided. Inject 1 mL Diluent (Sterile Water for Injection USP) for
1359 INTRON A into the INTRON A vial. Swirl gently to hasten complete dissolution of
1360 the powder. The appropriate INTRON A dose should then be withdrawn and
1361 injected into a 100-mL bag of 0.9% Sodium Chloride Injection USP. The final
1362 concentration of INTRON A should not be less than 10 million IU/100 mL.

1363 Please refer to the **MEDICATION GUIDE** for detailed, step-by-step instructions
1364 on how to inject the INTRON A dose. After preparation and administration of
1365 INTRON A, it is essential to follow the procedure for proper disposal of syringes and
1366 needles.

1367

1368 **INTRON A Solution for Injection in Vials**

1369

1370 INTRON A Solution for Injection is supplied in two multidose vials. The solutions for
1371 injection do not require reconstitution prior to administration; the solution is clear and
1372 colorless.

1373

1374 The appropriate dose should be withdrawn from the vial and injected
1375 intramuscularly, subcutaneously, or intralesionally.

1376

1377 **INTRON A Solution for Injection is not recommended for intravenous**
1378 **administration.**

1379

1380 **Solution for Injection in Multidose Pens**

1381

1382 The INTRON A Solution for Injection Multidose Pens are designed to deliver 3 to 12
1383 doses, depending on the individual dose, using a simple dial mechanism, and are for
1384 subcutaneous injections only. Only the needles provided in the packaging should be
1385 used for the INTRON A Solution for Injection Multidose Pen. A new needle is to be
1386 used each time a dose is delivered using the pen. To avoid the possible
1387 transmission of disease, each INTRON A Solution for Injection Multidose Pen is for
1388 single patient use only.

1389

1390 Please refer to the **MEDICATION GUIDE** for detailed, step-by-step instructions on
1391 how to inject the INTRON A dose. After preparation and administration of INTRON
1392 A, it is essential to follow the procedure for proper disposal of syringes and needles.

1393

1394 **HOW SUPPLIED**

1395

1396 **INTRON® A Powder for Injection**

1397 INTRON A Powder for Injection, 10 million IU per vial and Diluent for INTRON
 1398 A (Sterile Water for Injection USP) 1 mL per vial; boxes containing 1 INTRON A vial
 1399 and 1 vial of INTRON A Diluent (NDC 0085-0571-02).

1400 INTRON A Powder for Injection, 18 million IU per vial and Diluent for INTRON
 1401 A (Sterile Water for Injection USP) 1 mL per vial; boxes containing 1 vial of
 1402 INTRON A and 1 vial of INTRON A Diluent (NDC 0085-1110-01).

1403 INTRON A Powder for Injection, 50 million IU per vial and Diluent for INTRON
 1404 A (Sterile Water for Injection USP) 1 mL per vial; boxes containing 1 INTRON A vial
 1405 and 1 vial of INTRON A Diluent (NDC 0085-0539-01).

1406

1407 **INTRON A Solution for Injection in Multidose Pens**

1408 INTRON A Solution for Injection, 6 doses of 3 million IU (18 million IU)
 1409 Multidose Pen (22.5 million IU per 1.5 mL per pen); boxes containing 1 INTRON A
 1410 Multidose Pen, six disposable needles and alcohol swabs (NDC 0085-1242-01).

1411 INTRON A Solution for Injection, 6 doses of 5 million IU (30 million IU)
 1412 Multidose Pen (37.5 million IU per 1.5 mL per pen); boxes containing 1 INTRON A
 1413 Multidose Pen, six disposable needles and alcohol swabs (NDC 0085-1235-01).

1414 INTRON A Solution for Injection, 6 doses of 10 million IU (60 million IU)
 1415 Multidose Pen (75 million IU per 1.5 mL per pen); boxes containing 1 INTRON A
 1416 Multidose Pen, six disposable needles and alcohol swabs (NDC 0085-1254-01).

1417

1418 **INTRON A Solution for Injection in Vials**

1419 INTRON A Solution for Injection, 18 million IU multidose vial (22.8 million IU
 1420 per 3.8 mL per vial); boxes containing 1 vial of INTRON A Solution for Injection
 1421 (NDC 0085-1168-01).

1422 INTRON A Solution for Injection, 25 million IU multidose vial (32 million IU per
 1423 3.2 mL per vial); boxes containing 1 vial of INTRON A Solution for Injection (NDC
 1424 0085-1133-01).

1425

1426 **Storage**

1427

- 1428 • **INTRON A Powder for Injection/Reconstitution**

1429 INTRON A Powder for Injection should be stored in the refrigerator at 2° to
 1430 8°C (36°- 46°F). After reconstitution, the solution should be used
 1431 immediately, but may be stored up to 24 hours at 2° to 8°C (36°- 46°F).
 1432 Throw away any medicine left in the vial after you withdraw 1 dose.

- 1433 • **INTRON A Solution for Injection in Vials**

1434 INTRON A Solution for Injection in Vials should be stored in the refrigerator at
 1435 2° to 8°C (36°- 46°F).

- 1436 • **INTRON A Solution for Injection in Multidose Pens**

1437 INTRON A Solution for Injection in Multidose Pens should be stored in the
 1438 refrigerator at 2° to 8°C (36°- 46°F).

- 1439 • **INTRON A Solution for Injection and INTRON A Solution for Injection in
 1440 the Multidose Pens**

1441 INTRON A Solution for Injection and INTRON A Solution for Injection in the
 1442 Multidose Pens should not be frozen and should be kept away from heat.

1443 Throw away any unused INTRON A Multidose Pen remaining after 4 weeks.
1444 Throw away any unused INTRON A Solution for Injection remaining in the vial
1445 after one month.
1446

1447 **References:**

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1466 U.S. Patent Nos. 5,935,566 and 6,610,830.

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1468 Rev. 9/11

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