PRODUCT INFORMATION

INTRON® A

Interferon alfa-2b, recombinant
For Injection

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

DESCRIPTION

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

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

Powder for Injection

Vial Strength Million IU	mL Diluent	Final Concentration after Reconstitution million IU/mL*	mg INTRON A† per vial	Route of Administration
10	1	10	0.038	IM, SC, IV, IL
18	1	18	0.069	IM, SC, IV
50	1	50	0.192	IM, SC, IV

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

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

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

Solution Vials for Injection

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 x 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).

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

CLINICAL PHARMACOLOGY

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

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

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

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

Pharmacokinetics The pharmacokinetics of INTRON® A were studied in 12 healthy male volunteers following single doses of 5 million IU/m^2 administered intramuscularly, subcutaneously, and as a 30-minute intravenous infusion in a crossover design.

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

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

Urine INTRON A concentrations following a single dose (5 million IU/m^2) were not detectable after any of the parenteral routes of administration. This result was expected since preliminary studies with isolated and perfused rabbit kidneys have shown that the kidney may be the main site of interferon catabolism.

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

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

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

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

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

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

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

Malignant Melanoma The safety and efficacy of INTRON A was evaluated as adjuvant to surgical treatment in patients with melanoma who were free of disease (post surgery) but at high risk for systemic recurrence. These included patients with lesions of Breslow thickness greater than 4 mm, or patients with lesions of any Breslow thickness with primary or recurrent nodal involvement. In a randomized, controlled trial in 280 patients, 143 patients received INTRON A therapy at 20 million IU/m^2 intravenously five times per week for 4 weeks (induction phase) followed by 10 million IU/m^2 subcutaneously three times per week for 48 weeks (maintenance phase). In the clinical trial, the median daily INTRON A dose administered to patients was 19.1 million IU/m^2 during the induction phase and 9.1 million IU/m^2 during the maintenance phase. INTRON A therapy was begun less than or equal to 56 days after surgical resection. The remaining 137 patients were observed.

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

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

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

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

The group receiving the combination of INTRON A therapy plus CHVP had a significantly longer progression-free survival (2.9 years versus 1.5 years, *P*=0.0001, Log Rank test). After a median follow-up of 6.1 years, the median survival for patients treated with CHVP alone was 5.5 years while median survival for patients treated with CHVP plus INTRON A therapy had not been reached (*P*=0.004, Log Rank test). In three additional published, randomized, controlled studies of the addition of interferon alpha to anthracycline-containing combination chemotherapy regimens,[1-3] the addition of interferon alpha was associated with significantly prolonged progression-free survival. Differences in overall survival were not consistently observed.

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

INTRON A treatment of condylomata was significantly more effective than placebo, as measured by disappearance of lesions, decreases in lesion size, and by an

overall change in disease status. Of 192 INTRON A-treated patients and 206 placebo-treated patients who were evaluable for efficacy at the time of best response during the course of the study, 42% of INTRON A patients versus 17% of placebo patients experienced clearing of all treated lesions. Likewise, 24% of INTRON A patients versus 8% of placebo patients experienced marked (75% to less than 100%) reduction in lesion size, 18% versus 9% experienced moderate (50% to 75%) reduction in lesion size, 10% versus 42% had a slight (less than 50%) reduction in lesion size, 5% versus 24% had no change in lesion size, and 0% versus 1% experienced exacerbation ($P<0.001$).

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

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

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

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

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

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

In one study, INTRON A doses of 30 million IU/m^2 were administered subcutaneously three times per week (TIW) to patients with AIDS-Related KS. Doses were adjusted for patient tolerance. The average weekly dose delivered in the first 4 weeks was 150 million IU; at the end of 12 weeks this averaged 110 million IU/week; and by 24 weeks averaged 75 million IU/week.

Forty-four percent of asymptomatic patients responded versus 7% of symptomatic patients. The median time to response was approximately 2 months and 1 month, respectively, for asymptomatic and symptomatic patients. The median duration of response was approximately 3 months and 1 month, respectively, for the

asymptomatic and symptomatic patients. Baseline T4/T8 ratios were 0.46 for responders versus 0.33 for nonresponders.

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

In all studies, the likelihood of response was greatest in patients with relatively intact immune systems as assessed by baseline CD4 counts (interchangeable with T4 counts). Results at doses of 30 million IU/m^2 TIW and 35 million IU/QD were subcutaneously similar and are provided together in TABLE 1. This table demonstrates the relationship of response to baseline CD4 count in both asymptomatic and symptomatic patients in the 30 million IU/m^2 TIW and the 35 million IU/QD treatment groups.

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

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

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

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

In Study 1, all patients were initially treated with INTRON A 3 million IU TIW subcutaneously for 24 weeks (run-in-period). Patients who completed the initial 24-week treatment period were then randomly assigned to receive no further treatment, or to receive 3 million IU TIW for an additional 48 weeks. In Study 2, patients who met the entry criteria were randomly assigned to receive INTRON A 3 million IU TIW subcutaneously for 24 weeks or to receive INTRON A 3 million IU TIW subcutaneously

for 96 weeks. In both studies, patient follow-up was variable and some data collection was retrospective.

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

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

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

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

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

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

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

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

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

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

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

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

Pediatrics The safety and efficacy of INTRON A in the treatment of chronic hepatitis B was evaluated in one randomized controlled trial of 149 patients ranging from 1 year to 17 years of age. Seventy-two patients were treated with 3 million IU/m^2 of INTRON A therapy administered subcutaneously three times a week (TIW) for 1 week; the dose was then escalated to 6 million IU/m^2 TIW for a minimum of 16 weeks up to 24 weeks. The maximum weekly dosage was 10 million IU TIW. Seventy-seven patients were untreated controls. Study entry and response criteria were identical to those described in the adult patient population.

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

TABLE 1
RESPONSE BY BASELINE CD4 COUNT IN **AIDS-RELATED KS** PATIENTS*
30 million IU/m² TIW, SC and
35 million IU QD, SC

	Asymptomatic		*Symptomatic*	
CD4<200	4/14	(29%)	0/19	(0%)
200≤CD4≤400	6/12	(50%)	0/5	(0%)
		} 58%		
CD4>400	5/7	(71%)	0/0	(0%)

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

TABLE 2
SUSTAINED ALT RESPONSE RATE VERSUS DURATION OF THERAPY
*IN **CHRONIC HEPATITIS C** PATIENTS*
INTRON A 3 Million IU TIW
Treatment Group - Number of Patients (%)*

Study Number	*INTRON A 3 million IU 24 weeks of treatment*	*INTRON A 3 million IU 72 or 96 weeks of treatment†*	*Difference (Extended — 24 weeks) (95% CI)‡*
	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.

TABLE 3
VIROLOGIC RESPONSE IN **CHRONIC HEPATITIS B** PATIENTS*

Study Number	Treatment Group† - Number of Patients (%) INTRON A 5 million IU QD		INTRON A 10 million IU TIW		Untreated Controls		P‡ Value
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 post-therapy.
† Patients pretreated with prednisone not shown.
‡ INTRON A treatment group versus 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).

TABLE 4
ALT RESPONSES IN **CHRONIC HEPATITIS B** PATIENTS*
Treatment Group - Number of Patients (%)

Study Number	INTRON A 5 million IU QD		INTRON A 10 million IU TIW		Untreated Controls		P† Value
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 post-therapy.
† INTRON A treatment group versus 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).

INDICATIONS AND USAGE

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

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

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

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

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

AIDS-Related Kaposi's Sarcoma INTRON A is indicated for the treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. The likelihood of response to INTRON A therapy is greater in patients who are without systemic

symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count.

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

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

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other clinical signs of decompensation
- Bilirubin — Less than or equal to 2 mg/dL
- Albumin — Stable and within normal limits
- Prothrombin Time — Less than 3 seconds prolonged
- WBC — Greater than or equal to 3000/mm^3
- Platelets — Greater than or equal to 70,000/mm^3

Serum creatinine should be normal or near normal.

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

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

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

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

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

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other signs of clinical decompensation
- Bilirubin — Normal
- Albumin — Stable and within normal limits
- Prothrombin Time — *Adults* less than 3 seconds prolonged
  Pediatrics less than or equal to 2 seconds prolonged
- WBC — Greater than or equal to 4000/mm^3
- Platelets — *Adults* greater than or equal to 100,000/mm^3
  Pediatrics greater than or equal to 150,000/mm^3

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

A transient increase in ALT greater than or equal to 2 times baseline value (flare) can occur during INTRON A therapy for chronic hepatitis B. In clinical trials in adults and pediatrics, this flare generally occurred 8 to 12 weeks after initiation of therapy and was more frequent in responders (*adults* 63%, 24/38; *pediatrics* 59%, 10/17) than in nonresponders (*adults* 27%, 13/48; *pediatrics* 35%, 19/55). However, in adults and pediatrics, elevations in bilirubin greater than or equal to 3 mg/dL (greater than or equal to 2 times ULN) occurred infrequently (*adults* 2%, 2/86; *pediatrics* 3%, 2/72) during therapy. When ALT flare occurs, in general, INTRON A therapy should be continued

unless signs and symptoms of liver failure are observed. During ALT flare, clinical symptomatology and liver function tests including ALT, prothrombin time, alkaline phosphatase, albumin, and bilirubin, should be monitored at approximately 2-week intervals (see **WARNINGS**).

CONTRAINDICATIONS

INTRON® A is contraindicated in patients with:

- Hypersensitivity to interferon alpha or any component of the product
- Autoimmune hepatitis
- Decompensated liver disease

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

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

See REBETOL prescribing information for additional information.

WARNINGS

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

Cardiovascular Disorders

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

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

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

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

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

Treatment with interferons may be associated with exacerbated symptoms of psychiatric disorders in patients with co-occurring psychiatric and substance use disorders. If treatment with interferons is initiated in patients with prior history or existence of psychiatric condition or with a history of substance use disorders, treatment considerations should include the need for drug screening and periodic health evaluation, including psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance use is recommended.

Bone Marrow Toxicity
INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including aplastic anemia. It is advised that complete blood counts (CBC) be obtained pretreatment and monitored routinely during therapy (see **PRECAUTIONS, Laboratory Tests**). INTRON A therapy should be discontinued in patients who develop

severe decreases in neutrophil (less than 0.5 x 10^9/L) or platelet counts (less than 25 x 10^9/L) (see **DOSAGE AND ADMINISTRATION,** Guidelines for Dose Modification).

Ophthalmologic Disorders

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

Endocrine Disorders

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

Gastrointestinal Disorders

Hepatotoxicity, including fatality, has been observed in interferon alpha-treated patients, including those treated with INTRON A. INTRON A increases the risk of hepatic decompensation and death in patients with cirrhosis. Any patient developing liver function abnormalities during treatment should be monitored closely and if appropriate, treatment should be discontinued.

Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by INTRON A or other alpha interferons. Recurrence of respiratory failure has been observed with interferon rechallenge. The etiologic explanation for these pulmonary findings has yet to be established. Any patient developing fever, cough, dyspnea, or other respiratory symptoms should have a chest X-ray taken. If the chest X-ray shows pulmonary

infiltrates or there is evidence of pulmonary function impairment, the patient should be closely monitored, and, if appropriate, interferon alpha treatment should be discontinued. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha.

Autoimmune Disorders

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

Human Albumin

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

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

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

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

therapy, the potential risks must be evaluated against the potential benefits of treatment.

Peripheral Neuropathy

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

Use with Ribavirin (see also REBETOL® prescribing information) REBETOL may cause birth defects and/or death of the unborn child. REBETOL therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use at least two forms of contraception and have monthly pregnancy tests (see **CONTRAINDICATIONS** and **PRECAUTIONS**, **Information for Patients**).

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

PRECAUTIONS

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

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

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

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

Triglycerides Elevated triglyceride levels have been observed in patients treated with interferons, including INTRON A therapy. Elevated triglyceride levels should be managed as clinically appropriate. Hypertriglyceridemia may result in pancreatitis. Discontinuation of INTRON A therapy should be considered for patients with

persistently elevated triglycerides (e.g., triglycerides greater than 1000 mg/dL) associated with symptoms of potential pancreatitis, such as abdominal pain, nausea, or vomiting.

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

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

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

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

If a decision is made to allow a patient to self-administer INTRON A, they should be instructed, based on their treatment, if they should inject a dose of INTRON® A subcutaneously or intramuscularly. If it is too difficult for them to inject themselves, they should be instructed to ask someone who has been trained to give the injection to them. Patients should be instructed on the importance of site selection for self-administering the injection, as well as the importance on rotating the injection sites. A puncture resistant container for the disposal of needles and syringes should be supplied. Patients self-administering INTRON A should be instructed on the proper disposal of needles and syringes and cautioned against reuse.

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

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

- Standard hematologic tests — including hemoglobin, complete and differential white blood cell counts, and platelet count.
- Blood chemistries — electrolytes, liver function tests, and TSH.
- Monitor hepatic function with serum bilirubin, ALT (alanine transaminase), AST (aspartate aminotransferase), alkaline phosphatase, and LDH (lactate dehydrogenase) at 2, 8 and 12 weeks following initiation of INTRON A, then every 6 months while receiving INTRON A. Permanently discontinue INTRON A for evidence of severe (Grade 3) hepatic injury or hepatic decompensation (Child-Pugh score >6 [class B and C]).

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

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

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

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

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

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

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

Mutagenicity studies have demonstrated that INTRON A is not mutagenic.

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

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

INTRON A in combination with REBETOL should be used with caution in fertile men. See the REBETOL prescribing information for additional information.

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

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

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

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

Pediatric Use ***General*** Safety and effectiveness in pediatric patients have not been established for indications other than chronic hepatitis B and chronic hepatitis C.
Chronic Hepatitis B Safety and effectiveness in pediatric patients ranging in age from 1 to 17 years have been established based upon one controlled clinical trial (see **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE,** and **DOSAGE AND ADMINISTRATION, Chronic Hepatitis B Pediatrics**).
Chronic Hepatitis C Safety and effectiveness in pediatric patients ranging in age from 3 to 16 years have been established based upon clinical studies in 118 patients. See REBETOL prescribing information for additional information. Suicidal ideation or attempts occurred more frequently among pediatric patients compared to adult patients (2.4% versus 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.

Long-term data in a limited number of patients suggests that combination therapy may induce a growth inhibition that results in reduced final adult height in some patients (see **ADVERSE REACTIONS, Chronic Hepatitis C Pediatrics**).

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
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/m² Induction (IV) 10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*	*1 MIU/lesion*	*30 MIU/m² TIW/SC*	*35 MIU QD/SC*	*3 MIU TIW*	*5 MIU QD*	*10 MIU TIW*	*6 MIU/m² TIW*
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
Application-Site Disorders			20							
injection site	--	1	--	--	--	--	5	3	--	--

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/m² Induction (IV) 10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*	*1 MIU/lesion*	*30 MIU/m² TIW/SC*	*35 MIU QD/SC*	*3 MIU TIW*	*5 MIU QD*	*10 MIU TIW*	*6 MIU/m² TIW*
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
inflammation										
other (≤5%)	burning, injection site bleeding, injection site pain, injection site reaction (5% in chronic hepatitis B pediatrics), itching									
Blood Disorders (<5%)	anemia, anemia hypochromic, granulocytopenia, hemolytic anemia, leukopenia, lymphocytosis, neutropenia (9% in chronic hepatitis C, 14% in chronic hepatitis B pediatrics), thrombocytopenia (10% in chronic hepatitis C) (bleeding 8% in malignant melanoma), thrombocytopenia purpura									
Body as a Whole										
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									
Cardiovascular System Disorders (<5%)	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									
Endocrine System Disorders (<5%)	aggravation of diabetes mellitus, goiter, gynecomastia, hyperglycemia, hyperthyroidism, hypertriglyceridemia, hypothyroidism, virilism									
Flu-like Symptoms										
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									
Gastrointestinal System Disorders										
diarrhea	35	19	18	2	18	45	13	19	8	12
anorexia	69	21	19	1	38	41	14	43	53	43
nausea	66	24	21	17	28	21	19	50	33	18
taste alteration	24	2	13	<1	5	7	2	10	--	--
abdominal pain	2	20	<5	1	5	21	16	5	4	23
loose stools	--	1	--	<1	--	10	2	2	--	2
vomiting	†	32	6	2	11	14	8	7	10	27

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/m² Induction (IV) 10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*	*1 MIU/lesion*	*30 MIU/m² TIW/SC*	*35 MIU QD/SC*	*3 MIU TIW*	*5 MIU QD*	*10 MIU TIW*	*6 MIU/m² TIW*
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
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 Disorders (<5%)	amenorrhea (12% in follicular lymphoma), dysmenorrhea, impotence, leukorrhea, menorrhagia, menstrual irregularity, pelvic pain, penis disorder, sexual dysfunction, uterine bleeding, vaginal dryness									
Resistance Mechanism Disorders										
moniliasis	--	1	--	<1	--	17	--	--	--	--
herpes simplex	1	2	--	1	--	3	1	5	--	--

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/m² Induction (IV) 10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*	*1 MIU/lesion*	*30 MIU/m² TIW/SC*	*35 MIU QD/SC*	*3 MIU TIW*	*5 MIU QD*	*10 MIU TIW*	*6 MIU/m² TIW*
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
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

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

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

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

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

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

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

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

AIDS-Related Kaposi's Sarcoma In patients with AIDS-Related Kaposi's Sarcoma, some type of adverse reaction occurred in 100% of the 74 patients treated with 30 million IU/m^2 three times a week and in 97% of the 29 patients treated with 35 million IU per day.

Of these adverse reactions, those classified as severe (World Health Organization grade 3 or 4) were reported in 27% to 55% of patients. Severe adverse reactions in the 30 million IU/m^2 TIW study included: fatigue (20%), influenza-like symptoms (15%), anorexia (12%), dry mouth (4%), headache (4%), confusion (3%), fever (3%), myalgia (3%), and nausea and vomiting (1% each). Severe adverse reactions for patients who received the 35 million IU QD included: fever (24%), fatigue (17%), influenza-like symptoms (14%), dyspnea (14%), headache (10%), pharyngitis (7%), and ataxia, confusion, dysphagia, GI hemorrhage, abnormal hepatic function, increased SGOT, myalgia, cardiomyopathy, face edema, depression, emotional lability, suicide attempt, chest pain, and coughing (1 patient each). Overall, the incidence of severe toxicity was higher among patients who received the 35 million IU per day dose.

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

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

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

Chronic Hepatitis C *Pediatrics* In pediatric patients with chronic hepatitis C treated with INTRON A 3 MIU/m^2 three times weekly and REBETOL 15 mg/kg per day, all

subjects (n=118) had at least one adverse event during 24-48 weeks of treatment, of which 80% were considered to be mild or moderate in severity. Six percent discontinued therapy due to adverse reactions and dose modifications were required in 30% of subjects, most commonly for anemia and neutropenia. Adverse events occurring in more than 50% of subjects included headache, fever, fatigue and anorexia. Adverse events occurring in 20-50% of subjects included influenza-like symptoms, abdominal pain, vomiting, nausea, myalgia, pharyngitis, diarrhea, viral infection, rigors, weight decrease, musculoskeletal pain, alopecia and dizziness. The most common laboratory test abnormalities were neutropenia (34%) and anemia (27%). Depression was reported in 13% (n=15) of children. Three of these subjects had suicidal ideation, and one attempted suicide. Weight loss and slowed growth are common in pediatric patients during combination therapy with INTRON A and REBETOL. Following treatment, rebound growth and weight gain occurred in most subjects. Long-term follow-up data in pediatric subjects, however, indicates that INTRON A in combination with REBETOL may induce a growth inhibition that results in reduced adult height in some patients (see **PRECAUTIONS, Pediatric Use)**.

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

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

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

Chronic Hepatitis B *Pediatrics* In pediatric patients with chronic hepatitis B (n=72) during 16-24 weeks of treatment, the most frequently reported adverse events were those commonly associated with interferon treatment: flu-like symptoms (100%), gastrointestinal system disorders (46%), and nausea and vomiting (40%). Neutropenia (13%) and thrombocytopenia (3%) were also reported. None of the adverse events was life threatening and most were moderate to severe and resolved upon dose reduction or drug discontinuation.

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		CHRONIC HEPATITIS B 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/mm^3

‡ Decrease to <70,000/mm^3

§ Neutrophils plus bands

‖ White Blood Cell Count was reported as neutropenia

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

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

Blood and Lymphatic System Disorders
pancytopenia (concurrent anemia, leukopenia, thrombocytopenia), aplastic anemia, pure red cell aplasia, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura
Ear and Labyrinth Disorders
hearing loss
Endocrine Disorders
hypopituitarism
Eye Disorders
Vogt-Koyanagi-Harada syndrome, serous retinal detachment
Gastrointestinal Disorders
pancreatitis
General Disorders and Administration Site Conditions
asthenic conditions (including asthenia, malaise, fatigue)
Immune System Disorders
cases of acute hypersensitivity reactions, including anaphylaxis and angioedema, systemic lupus erythematosus, sarcoidosis or exacerbation of sarcoidosis
Musculoskeletal and Connective Tissue Disorders
myositis
Nervous System Disorders
peripheral neuropathy
Psychiatric Disorders
homicidal ideation, psychosis including hallucinations
Renal and Urinary Disorders
renal failure, renal insufficiency, nephrotic syndrome
Respiratory, Thoracic, and Mediastinal Disorders
pulmonary hypertension, pulmonary fibrosis
Skin and Subcutaneous Tissue Disorders
injection site necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, urticaria

OVERDOSAGE

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

because interferons are poorly absorbed orally. Consultation with a poison center is recommended.

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

DOSAGE AND ADMINISTRATION

General

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

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

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

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

Hairy Cell Leukemia (see DOSAGE AND ADMINISTRATION, General)

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

Dosage Forms for This Indication

Dosage Form	Concentration	Route	Fixed Doses
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

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

Dose Adjustment:

- If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy should be temporarily withheld until the adverse reactions abate and then resume at 50% (1 MIU/m^2 TIW).

- If severe adverse reactions persist or recur following dosage adjustment, INTRON A should be permanently discontinued.
- INTRON A should be discontinued for progressive disease or failure to respond after six months of treatment.

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

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

Induction Recommended Dose: The recommended daily dose of INTRON A in induction is 20 million IU/m^2 as an intravenous infusion, over 20 minutes, 5 consecutive days per week, for 4 weeks (see ***Dose Adjustment*** below).

Dosage Forms for This Indication

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

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

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

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

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

Maintenance Recommended Dose: The recommended dose of INTRON A for maintenance is 10 million IU/m^2 as a subcutaneous injection three times per week for 48 weeks (see ***Dose Adjustment*** below).

Dosage Forms for This Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single dose)*	10 MIU/mL	SC	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

*Patients receiving 50% dose reduction only
**Patients receiving full dose only

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.
Dose Adjustment: **NOTE:** Regular laboratory testing should be performed to monitor laboratory abnormalities for the purpose of dose modifications (see **PRECAUTIONS, Laboratory Tests**).

- INTRON A should be withheld for severe adverse reactions, including granulocyte counts greater than 250/mm^3 but less than 500/mm^3 or SGPT/SGOT greater than 5-10x upper limit of normal, until adverse reactions abate. INTRON A treatment should be restarted at 50% of the previous dose.

- INTRON A should be permanently discontinued for:
  - Toxicity that does not abate after withholding INTRON A
  - Severe adverse reactions which recur in patients receiving reduced doses of INTRON A
  - Granulocyte count less than 250/mm^3 or SGPT/SGOT of greater than 10x upper limit of normal

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

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

Dosage Forms for This Indication

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

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

Dose Adjustment:

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

- Delay chemotherapy cycle if neutrophil count was less than 1500/mm^3 or platelet count was less than 75,000/mm^3.
- 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**).
- Administration of INTRON A therapy should be withheld for a neutrophil count less than 1000/mm^3, or a platelet count less than 50,000/mm^3.
- INTRON A dose should be reduced by 50% (2.5 MIU TIW) for a neutrophil count greater than 1000/mm^3, but less than 1500/mm^3. 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/mm^3).

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

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

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

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

NOTE: Do not use the following formulations for this indication:
- **the 18 million or 50 million IU Powder for Injection**
- **the 18 million IU multidose INTRON A Solution for Injection**

Dose Adjustment*:* None

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

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

Dose*:* The recommended dose of INTRON A for Kaposi's Sarcoma is 30 million IU/m^2/dose administered subcutaneously or intramuscularly three times a week until

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

Dosage Forms for This Indication

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

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

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

Dose Adjustment*:*

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

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

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

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

Dosage Forms for This Indication

Dosage Form	Concentration	Route	Fixed Doses
Solution 18 MIU multidose	6 MIU/mL	IM, SC	N/A

Dose Adjustment*:* If severe adverse reactions develop during INTRON A treatment, the dose should be modified (50% reduction) or therapy should be temporarily

discontinued until the adverse reactions abate. If intolerance persists after dose adjustment, INTRON A therapy should be discontinued.

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

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

Dosage Forms for This Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single dose)	10 MIU/mL	IM, SC	N/A
Solution 25 MIU multidose	10 MIU/mL	IM, SC	N/A

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

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

Dose: The recommended dose of INTRON A for the treatment of chronic hepatitis B is 3 million IU/m^2 three times a week (TIW) for the first week of therapy followed by dose escalation to 6 million IU/m^2 TIW (maximum of 10 million IU TIW) administered subcutaneously for a total duration of 16 to 24 weeks.

Dosage Forms for This Indication

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

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

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

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

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

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

PREPARATION AND ADMINISTRATION Reconstitution of INTRON® A Powder for Injection The reconstituted solution is clear and colorless to light yellow. The INTRON A powder reconstituted with Sterile Water for Injection USP is a single-use vial and does not contain a preservative. **DO 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.

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

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).

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

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

- ***Intravenous Infusion***

The infusion solution should be prepared immediately prior to use. Based on the desired dose, the appropriate vial strength(s) of INTRON A should be reconstituted with the diluent provided. Inject 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 into a 100-mL bag of 0.9% Sodium Chloride Injection USP. The final concentration of INTRON A should not be less than 10 million IU/100 mL.

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

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

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

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

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

HOW SUPPLIED

INTRON® A Powder for Injection

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

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

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

INTRON A Solution for Injection in Vials

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

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

Storage

- **INTRON A Powder for Injection/Reconstitution**
  INTRON A Powder for Injection should be stored in the refrigerator at 2° to 8°C (36°-46°F). After reconstitution, the solution should be used immediately, but may be stored up to 24 hours at 2° to 8°C (36°-46°F). Throw away any medicine left in the vial after you withdraw 1 dose.
- **INTRON A Solution for Injection in Vials**
  INTRON A Solution for Injection in vials should be stored in the refrigerator at 2° to 8°C (36°-46°F).
  INTRON A Solution for Injection should not be frozen and should be kept away from heat. Throw away any unused INTRON A Solution for Injection remaining in the vial after one month.

References:

1. Smalley R, et al. *N Engl J Med.* 1992;327:1336-1341.
2. Aviles A, et al. *Leukemia and Lymphoma.* 1996;20:495-499.
3. Unterhalt M, et al. *Blood.* 1996;88(10 Suppl 1):1744A.
4. Schiller J, et al. *J Biol Response Mod.* 1989;8:252-261.
5. Poynard T, et al. *N Engl J Med.* 1995;332(22)1457-1462.
6. Lin R, et al. *J Hepatol.* 1995;23:487-496.

7. Perrillo R, et al. *N Engl J Med.* 1990;323:295-301.

8. Perez V, et al. *J Hepatol.* 1990;11:S113-S117.

9. Knodell R, et al. *Hepatology.* 1981;1:431-435.

10. Perrillo R, et al. *Ann Intern Med.* 1991;115:113-115.

11. Kauppila A, et al. *Int J Cancer.* 1982;29:291-294.

Manufactured by: Schering Corporation, a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889 USA.

For patent information: www.merck.com/product/patent/home.html

Copyright © 1986, 2011 Schering Corporation, a subsidiary of **Merck & Co., Inc.** All rights reserved.

Rev. 05/2015

uspi-mk2958-mtl-1ml-XXXXrXXX

PRODUCT INFORMATION

INTRON® A

Interferon alfa-2b, recombinant
For Injection

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

DESCRIPTION

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

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

Powder for Injection

Vial Strength Million IU	mL Diluent	Final Concentration after Reconstitution million IU/mL*	mg INTRON A† per vial	Route of Administration
10	1	10	0.038	IM, SC, IV, IL
18	1	18	0.069	IM, SC, IV
50	1	50	0.192	IM, SC, IV

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

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

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

Solution Vials for Injection

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 x 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).

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

CLINICAL PHARMACOLOGY

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

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

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

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

Pharmacokinetics The pharmacokinetics of INTRON® A were studied in 12 healthy male volunteers following single doses of 5 million IU/m^2 administered intramuscularly, subcutaneously, and as a 30-minute intravenous infusion in a crossover design.

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

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

Urine INTRON A concentrations following a single dose (5 million IU/m^2) were not detectable after any of the parenteral routes of administration. This result was expected since preliminary studies with isolated and perfused rabbit kidneys have shown that the kidney may be the main site of interferon catabolism.

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

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

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

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

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

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

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

Malignant Melanoma The safety and efficacy of INTRON A was evaluated as adjuvant to surgical treatment in patients with melanoma who were free of disease (post surgery) but at high risk for systemic recurrence. These included patients with lesions of Breslow thickness greater than 4 mm, or patients with lesions of any Breslow thickness with primary or recurrent nodal involvement. In a randomized, controlled trial in 280 patients, 143 patients received INTRON A therapy at 20 million IU/m^2 intravenously five times per week for 4 weeks (induction phase) followed by 10 million IU/m^2 subcutaneously three times per week for 48 weeks (maintenance phase). In the clinical trial, the median daily INTRON A dose administered to patients was 19.1 million IU/m^2 during the induction phase and 9.1 million IU/m^2 during the maintenance phase. INTRON A therapy was begun less than or equal to 56 days after surgical resection. The remaining 137 patients were observed.

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

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

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

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

The group receiving the combination of INTRON A therapy plus CHVP had a significantly longer progression-free survival (2.9 years versus 1.5 years, *P*=0.0001, Log Rank test). After a median follow-up of 6.1 years, the median survival for patients treated with CHVP alone was 5.5 years while median survival for patients treated with CHVP plus INTRON A therapy had not been reached (*P*=0.004, Log Rank test). In three additional published, randomized, controlled studies of the addition of interferon alpha to anthracycline-containing combination chemotherapy regimens,[1-3] the addition of interferon alpha was associated with significantly prolonged progression-free survival. Differences in overall survival were not consistently observed.

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

INTRON A treatment of condylomata was significantly more effective than placebo, as measured by disappearance of lesions, decreases in lesion size, and by an

overall change in disease status. Of 192 INTRON A-treated patients and 206 placebo-treated patients who were evaluable for efficacy at the time of best response during the course of the study, 42% of INTRON A patients versus 17% of placebo patients experienced clearing of all treated lesions. Likewise, 24% of INTRON A patients versus 8% of placebo patients experienced marked (75% to less than 100%) reduction in lesion size, 18% versus 9% experienced moderate (50% to 75%) reduction in lesion size, 10% versus 42% had a slight (less than 50%) reduction in lesion size, 5% versus 24% had no change in lesion size, and 0% versus 1% experienced exacerbation ($P<0.001$).

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

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

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

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

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

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

In one study, INTRON A doses of 30 million IU/m^2 were administered subcutaneously three times per week (TIW) to patients with AIDS-Related KS. Doses were adjusted for patient tolerance. The average weekly dose delivered in the first 4 weeks was 150 million IU; at the end of 12 weeks this averaged 110 million IU/week; and by 24 weeks averaged 75 million IU/week.

Forty-four percent of asymptomatic patients responded versus 7% of symptomatic patients. The median time to response was approximately 2 months and 1 month, respectively, for asymptomatic and symptomatic patients. The median duration of response was approximately 3 months and 1 month, respectively, for the

asymptomatic and symptomatic patients. Baseline T4/T8 ratios were 0.46 for responders versus 0.33 for nonresponders.

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

In all studies, the likelihood of response was greatest in patients with relatively intact immune systems as assessed by baseline CD4 counts (interchangeable with T4 counts). Results at doses of 30 million IU/m^2 TIW and 35 million IU/QD were subcutaneously similar and are provided together in TABLE 1. This table demonstrates the relationship of response to baseline CD4 count in both asymptomatic and symptomatic patients in the 30 million IU/m^2 TIW and the 35 million IU/QD treatment groups.

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

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

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

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

In Study 1, all patients were initially treated with INTRON A 3 million IU TIW subcutaneously for 24 weeks (run-in-period). Patients who completed the initial 24-week treatment period were then randomly assigned to receive no further treatment, or to receive 3 million IU TIW for an additional 48 weeks. In Study 2, patients who met the entry criteria were randomly assigned to receive INTRON A 3 million IU TIW subcutaneously for 24 weeks or to receive INTRON A 3 million IU TIW subcutaneously

for 96 weeks. In both studies, patient follow-up was variable and some data collection was retrospective.

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

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

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

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

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

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

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

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

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

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

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

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

Pediatrics The safety and efficacy of INTRON A in the treatment of chronic hepatitis B was evaluated in one randomized controlled trial of 149 patients ranging from 1 year to 17 years of age. Seventy-two patients were treated with 3 million IU/m^2 of INTRON A therapy administered subcutaneously three times a week (TIW) for 1 week; the dose was then escalated to 6 million IU/m^2 TIW for a minimum of 16 weeks up to 24 weeks. The maximum weekly dosage was 10 million IU TIW. Seventy-seven patients were untreated controls. Study entry and response criteria were identical to those described in the adult patient population.

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

TABLE 1
RESPONSE BY BASELINE CD4 COUNT IN **AIDS-RELATED KS** PATIENTS*
30 million IU/m² TIW, SC and
35 million IU QD, SC

	Asymptomatic		*Symptomatic*	
CD4<200	4/14	(29%)	0/19	(0%)
200≤CD4≤400	6/12	(50%)	0/5	(0%)
		} 58%		
CD4>400	5/7	(71%)	0/0	(0%)

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

TABLE 2
SUSTAINED ALT RESPONSE RATE VERSUS DURATION OF THERAPY
*IN **CHRONIC HEPATITIS C** PATIENTS*
INTRON A 3 Million IU TIW
Treatment Group - Number of Patients (%)*

Study Number	*INTRON A 3 million IU 24 weeks of treatment*	*INTRON A 3 million IU 72 or 96 weeks of treatment†*	*Difference (Extended — 24 weeks) (95% CI)‡*
	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.

TABLE 3
VIROLOGIC RESPONSE IN **CHRONIC HEPATITIS B** PATIENTS*

Study Number	Treatment Group† - Number of Patients (%) INTRON A 5 million IU QD		INTRON A 10 million IU TIW		Untreated Controls		P‡ Value
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 post-therapy.
† Patients pretreated with prednisone not shown.
‡ INTRON A treatment group versus 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).

TABLE 4
ALT RESPONSES IN **CHRONIC HEPATITIS B** PATIENTS*
Treatment Group - Number of Patients (%)

Study Number	INTRON A 5 million IU QD		INTRON A 10 million IU TIW		Untreated Controls		P† Value
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 post-therapy.
† INTRON A treatment group versus 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).

INDICATIONS AND USAGE

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

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

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

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

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

AIDS-Related Kaposi's Sarcoma INTRON A is indicated for the treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. The likelihood of response to INTRON A therapy is greater in patients who are without systemic

symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count.

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

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

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other clinical signs of decompensation
- Bilirubin — Less than or equal to 2 mg/dL
- Albumin — Stable and within normal limits
- Prothrombin Time — Less than 3 seconds prolonged
- WBC — Greater than or equal to 3000/mm^3
- Platelets — Greater than or equal to 70,000/mm^3

Serum creatinine should be normal or near normal.

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

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

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

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

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

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other signs of clinical decompensation
- Bilirubin — Normal
- Albumin — Stable and within normal limits
- Prothrombin Time — *Adults* less than 3 seconds prolonged
  Pediatrics less than or equal to 2 seconds prolonged
- WBC — Greater than or equal to 4000/mm^3
- Platelets — *Adults* greater than or equal to 100,000/mm^3
  Pediatrics greater than or equal to 150,000/mm^3

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

A transient increase in ALT greater than or equal to 2 times baseline value (flare) can occur during INTRON A therapy for chronic hepatitis B. In clinical trials in adults and pediatrics, this flare generally occurred 8 to 12 weeks after initiation of therapy and was more frequent in responders (*adults* 63%, 24/38; *pediatrics* 59%, 10/17) than in nonresponders (*adults* 27%, 13/48; *pediatrics* 35%, 19/55). However, in adults and pediatrics, elevations in bilirubin greater than or equal to 3 mg/dL (greater than or equal to 2 times ULN) occurred infrequently (*adults* 2%, 2/86; *pediatrics* 3%, 2/72) during therapy. When ALT flare occurs, in general, INTRON A therapy should be continued

unless signs and symptoms of liver failure are observed. During ALT flare, clinical symptomatology and liver function tests including ALT, prothrombin time, alkaline phosphatase, albumin, and bilirubin, should be monitored at approximately 2-week intervals (see **WARNINGS**).

CONTRAINDICATIONS

INTRON® A is contraindicated in patients with:

- Hypersensitivity to interferon alpha or any component of the product
- Autoimmune hepatitis
- Decompensated liver disease

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

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

See REBETOL prescribing information for additional information.

WARNINGS

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

Cardiovascular Disorders

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

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

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

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

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

Treatment with interferons may be associated with exacerbated symptoms of psychiatric disorders in patients with co-occurring psychiatric and substance use disorders. If treatment with interferons is initiated in patients with prior history or existence of psychiatric condition or with a history of substance use disorders, treatment considerations should include the need for drug screening and periodic health evaluation, including psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance use is recommended.

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

Ophthalmologic Disorders

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

Endocrine Disorders

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

Gastrointestinal Disorders

Hepatotoxicity, including fatality, has been observed in interferon alpha-treated patients, including those treated with INTRON A. INTRON A increases the risk of hepatic decompensation and death in patients with cirrhosis. Any patient developing liver function abnormalities during treatment should be monitored closely and if appropriate, treatment should be discontinued.

Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by INTRON A or other alpha interferons. Recurrence of respiratory failure has been observed with interferon rechallenge. The etiologic explanation for these pulmonary findings has yet to be established. Any patient developing fever, cough, dyspnea, or other respiratory symptoms should have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient should be closely monitored, and, if appropriate, interferon alpha treatment should be

discontinued. While this has been reported more often in patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha.

Autoimmune Disorders

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

Human Albumin

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

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

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

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

Peripheral Neuropathy

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

Use with Ribavirin (see also REBETOL® prescribing information) REBETOL may cause birth defects and/or death of the unborn child. REBETOL therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use at least two forms of contraception and have monthly pregnancy tests (see **CONTRAINDICATIONS** and **PRECAUTIONS**, **Information for Patients**).

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

PRECAUTIONS

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

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

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

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

Triglycerides Elevated triglyceride levels have been observed in patients treated with interferons, including INTRON A therapy. Elevated triglyceride levels should be managed as clinically appropriate. Hypertriglyceridemia may result in pancreatitis. Discontinuation of INTRON A therapy should be considered for patients with persistently elevated triglycerides (e.g., triglycerides greater than 1000 mg/dL)

associated with symptoms of potential pancreatitis, such as abdominal pain, nausea, or vomiting.

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

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

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

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

If a decision is made to allow a patient to self-administer INTRON A, they should be instructed, based on their treatment, if they should inject a dose of INTRON® A subcutaneously or intramuscularly. If it is too difficult for them to inject themselves, they should be instructed to ask someone who has been trained to give the injection to them. Patients should be instructed on the importance of site selection for self-administering the injection, as well as the importance on rotating the injection sites. A puncture resistant container for the disposal of needles and syringes should be supplied. Patients self-administering INTRON A should be instructed on the proper disposal of needles and syringes and cautioned against reuse.

Patients should be instructed that the Sterile Water for Injection vial supplied with Intron A Powder for Injection contains an excess amount of diluent (5 mL) and only 1 mL should be withdrawn to reconstitute Intron A Powder for Injection. The vial of Sterile Water for Injection is intended for single use only. Discard the unused portion of sterile water. Do not save or reuse.

Dental and Periodontal Disorders Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth

during long-term treatment with the combination of REBETOL and interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition, some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

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

- Standard hematologic tests — including hemoglobin, complete and differential white blood cell counts, and platelet count.
- Blood chemistries — electrolytes, liver function tests, and TSH.
- Monitor hepatic function with serum bilirubin, ALT (alanine transaminase), AST (aspartate aminotransferase), alkaline phosphatase, and LDH (lactate dehydrogenase) at 2, 8 and 12 weeks following initiation of INTRON A, then every 6 months while receiving INTRON A. Permanently discontinue INTRON A for evidence of severe (Grade 3) hepatic injury or hepatic decompensation (Child-Pugh score >6 [class B and C]).

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

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

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

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

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

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

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

Mutagenicity studies have demonstrated that INTRON A is not mutagenic.

Studies in mice (0.1, 1.0 million IU/day), rats (4, 20, 100 million IU/kg/day), and cynomolgus monkeys (1.1 million IU/kg/day; 0.25, 0.75, 2.5 million IU/kg/day) injected with INTRON A for up to 9 days, 3 months, and 1 month, respectively, have revealed no

evidence of toxicity. However, in cynomolgus monkeys (4, 20, 100 million IU/kg/day) injected daily for 3 months with INTRON A, toxicity was observed at the mid and high doses and mortality was observed at the high dose.

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

INTRON A in combination with REBETOL should be used with caution in fertile men. See the REBETOL prescribing information for additional information.

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

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

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

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

Pediatric Use ***General*** Safety and effectiveness in pediatric patients have not been established for indications other than chronic hepatitis B and chronic hepatitis C.
Chronic Hepatitis B Safety and effectiveness in pediatric patients ranging in age from 1 to 17 years have been established based upon one controlled clinical trial (see **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE,** and **DOSAGE AND ADMINISTRATION, Chronic Hepatitis B Pediatrics**).
Chronic Hepatitis C Safety and effectiveness in pediatric patients ranging in age from 3 to 16 years have been established based upon clinical studies in 118 patients. See REBETOL prescribing information for additional information. Suicidal ideation or attempts occurred more frequently among pediatric patients compared to adult patients (2.4% versus 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.

Long-term data in a limited number of patients suggests that combination therapy may induce a growth inhibition that results in reduced final adult height in some patients (see **ADVERSE REACTIONS, Chronic Hepatitis C Pediatrics**).

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
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/m² Induction (IV) 10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*	*1 MIU/lesion*	*30 MIU/m² TIW/SC*	*35 MIU QD/SC*	*3 MIU TIW*	*5 MIU QD*	*10 MIU TIW*	*6 MIU/m² TIW*

ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
Application-Site Disorders			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									
Blood Disorders (<5%)	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									
Body as a Whole										
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									
Cardiovascular System Disorders (<5%)	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									
Endocrine System Disorders (<5%)	aggravation of diabetes mellitus, goiter, gynecomastia, hyperglycemia, hyperthyroidism, hypertriglyceridemia, hypothyroidism, virilism									
Flu-like Symptoms										
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									
Gastrointestinal System Disorders										
diarrhea	35	19	18	2	18	45	13	19	8	12
anorexia	69	21	19	1	38	41	14	43	53	43
nausea	66	24	21	17	28	21	19	50	33	18
taste alteration	24	2	13	<1	5	7	2	10	--	--
abdominal pain	2	20	<5	1	5	21	16	5	4	23
loose stools	--	1	--	<1	--	10	2	2	--	2
vomiting	†	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										

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/m² Induction (IV) 10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*	*1 MIU/lesion*	*30 MIU/m² TIW/SC*	*35 MIU QD/SC*	*3 MIU TIW*	*5 MIU QD*	*10 MIU TIW*	*6 MIU/m² TIW*
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
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 Disorders (<5%)	amenorrhea (12% in follicular lymphoma), dysmenorrhea, impotence, leukorrhea, menorrhagia, menstrual irregularity, pelvic pain, penis disorder, sexual dysfunction, uterine bleeding, vaginal dryness									
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,									

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/m² Induction (IV) 10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*	*1 MIU/lesion*	*30 MIU/m² TIW/SC*	*35 MIU QD/SC*	*3 MIU TIW*	*5 MIU QD*	*10 MIU TIW*	*6 MIU/m² TIW*
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
	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

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

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

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

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

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

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

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

AIDS-Related Kaposi's Sarcoma In patients with AIDS-Related Kaposi's Sarcoma, some type of adverse reaction occurred in 100% of the 74 patients treated with 30 million IU/m^2 three times a week and in 97% of the 29 patients treated with 35 million IU per day.

Of these adverse reactions, those classified as severe (World Health Organization grade 3 or 4) were reported in 27% to 55% of patients. Severe adverse reactions in the 30 million IU/m^2 TIW study included: fatigue (20%), influenza-like symptoms (15%), anorexia (12%), dry mouth (4%), headache (4%), confusion (3%), fever (3%), myalgia (3%), and nausea and vomiting (1% each). Severe adverse reactions for patients who received the 35 million IU QD included: fever (24%), fatigue (17%), influenza-like symptoms (14%), dyspnea (14%), headache (10%), pharyngitis (7%), and ataxia, confusion, dysphagia, GI hemorrhage, abnormal hepatic function, increased SGOT, myalgia, cardiomyopathy, face edema, depression, emotional lability, suicide attempt, chest pain, and coughing (1 patient each). Overall, the incidence of severe toxicity was higher among patients who received the 35 million IU per day dose.

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

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

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

Chronic Hepatitis C *Pediatrics* In pediatric patients with chronic hepatitis C treated with INTRON A 3 MIU/m^2 three times weekly and REBETOL 15 mg/kg per day, all

subjects (n=118) had at least one adverse event during 24-48 weeks of treatment, of which 80% were considered to be mild or moderate in severity. Six percent discontinued therapy due to adverse reactions and dose modifications were required in 30% of subjects, most commonly for anemia and neutropenia. Adverse events occurring in more than 50% of subjects included headache, fever, fatigue and anorexia. Adverse events occurring in 20-50% of subjects included influenza-like symptoms, abdominal pain, vomiting, nausea, myalgia, pharyngitis, diarrhea, viral infection, rigors, weight decrease, musculoskeletal pain, alopecia and dizziness. The most common laboratory test abnormalities were neutropenia (34%) and anemia (27%). Depression was reported in 13% (n=15) of children. Three of these subjects had suicidal ideation, and one attempted suicide. Weight loss and slowed growth are common in pediatric patients during combination therapy with INTRON A and REBETOL. Following treatment, rebound growth and weight gain occurred in most subjects. Long-term follow-up data in pediatric subjects, however, indicates that INTRON A in combination with REBETOL may induce a growth inhibition that results in reduced adult height in some patients (see **PRECAUTIONS, Pediatric Use)**.

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

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

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

Chronic Hepatitis B *Pediatrics* In pediatric patients with chronic hepatitis B (n=72) during 16-24 weeks of treatment, the most frequently reported adverse events were those commonly associated with interferon treatment: flu-like symptoms (100%), gastrointestinal system disorders (46%), and nausea and vomiting (40%). Neutropenia (13%) and thrombocytopenia (3%) were also reported. None of the adverse events was life threatening and most were moderate to severe and resolved upon dose reduction or drug discontinuation.

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		CHRONIC HEPATITIS B 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/mm^3

‡ Decrease to <70,000/mm^3

§ Neutrophils plus bands

‖ White Blood Cell Count was reported as neutropenia

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

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

Blood and Lymphatic System Disorders
pancytopenia (concurrent anemia, leukopenia, thrombocytopenia), aplastic anemia, pure red cell aplasia, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura
Ear and Labyrinth Disorders
hearing loss
Endocrine Disorders
hypopituitarism
Eye Disorders
Vogt-Koyanagi-Harada syndrome, serous retinal detachment
Gastrointestinal Disorders
pancreatitis
General Disorders and Administration Site Conditions
asthenic conditions (including asthenia, malaise, fatigue)
Immune System Disorders
cases of acute hypersensitivity reactions, including anaphylaxis and angioedema, systemic lupus erythematosus, sarcoidosis or exacerbation of sarcoidosis
Musculoskeletal and Connective Tissue Disorders
myositis
Nervous System Disorders
peripheral neuropathy
Psychiatric Disorders
homicidal ideation, psychosis including hallucinations
Renal and Urinary Disorders
renal failure, renal insufficiency, nephrotic syndrome
Respiratory, Thoracic, and Mediastinal Disorders
pulmonary hypertension, pulmonary fibrosis
Skin and Subcutaneous Tissue Disorders
injection site necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, urticaria

OVERDOSAGE

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

because interferons are poorly absorbed orally. Consultation with a poison center is recommended.

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

DOSAGE AND ADMINISTRATION

General

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

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

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

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

Hairy Cell Leukemia (see DOSAGE AND ADMINISTRATION, General)

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

Dosage Forms for This Indication

Dosage Form	Concentration	Route	Fixed Doses
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

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

Dose Adjustment:

- If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy should be temporarily withheld until the adverse reactions abate and then resume at 50% (1 MIU/m^2 TIW).

- If severe adverse reactions persist or recur following dosage adjustment, INTRON A should be permanently discontinued.
- INTRON A should be discontinued for progressive disease or failure to respond after six months of treatment.

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

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

Induction Recommended Dose: The recommended daily dose of INTRON A in induction is 20 million IU/m^2 as an intravenous infusion, over 20 minutes, 5 consecutive days per week, for 4 weeks (see ***Dose Adjustment*** below).

Dosage Forms for This Indication

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

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

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

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

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

Maintenance Recommended Dose: The recommended dose of INTRON A for maintenance is 10 million IU/m^2 as a subcutaneous injection three times per week for 48 weeks (see ***Dose Adjustment*** below).

Dosage Forms for This Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single dose)*	10 MIU/mL	SC	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

*Patients receiving 50% dose reduction only
**Patients receiving full dose only

NOTE: INTRON A Powder for Injection does not contain a preservative. The vial must be discarded after reconstitution and withdrawal of a single dose.
Dose Adjustment: **NOTE:** Regular laboratory testing should be performed to monitor laboratory abnormalities for the purpose of dose modifications (see **PRECAUTIONS, Laboratory Tests**).

- INTRON A should be withheld for severe adverse reactions, including granulocyte counts greater than 250/mm^3 but less than 500/mm^3 or SGPT/SGOT greater than 5-10x upper limit of normal, until adverse reactions abate. INTRON A treatment should be restarted at 50% of the previous dose.

- INTRON A should be permanently discontinued for:
  - Toxicity that does not abate after withholding INTRON A
  - Severe adverse reactions which recur in patients receiving reduced doses of INTRON A
  - Granulocyte count less than 250/mm^3 or SGPT/SGOT of greater than 10x upper limit of normal

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

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

Dosage Forms for This Indication

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

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

Dose Adjustment:

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

- Delay chemotherapy cycle if neutrophil count was less than 1500/mm^3 or platelet count was less than 75,000/mm^3.
- 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**).
- Administration of INTRON A therapy should be withheld for a neutrophil count less than 1000/mm^3, or a platelet count less than 50,000/mm^3.
- INTRON A dose should be reduced by 50% (2.5 MIU TIW) for a neutrophil count greater than 1000/mm^3, but less than 1500/mm^3. 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/mm^3).

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

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

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

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

NOTE: Do not use the following formulations for this indication:
- **the 18 million or 50 million IU Powder for Injection**
- **the 18 million IU multidose INTRON A Solution for Injection**

Dose Adjustment*:* None

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

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

Dose*:* The recommended dose of INTRON A for Kaposi's Sarcoma is 30 million IU/m^2/dose administered subcutaneously or intramuscularly three times a week until

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

Dosage Forms for This Indication

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

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

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

Dose Adjustment*:*

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

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

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

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

Dosage Forms for This Indication

Dosage Form	Concentration	Route	Fixed Doses
Solution 18 MIU multidose	6 MIU/mL	IM, SC	N/A

Dose Adjustment*:* If severe adverse reactions develop during INTRON A treatment, the dose should be modified (50% reduction) or therapy should be temporarily

discontinued until the adverse reactions abate. If intolerance persists after dose adjustment, INTRON A therapy should be discontinued.

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

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

Dosage Forms for This Indication

Dosage Form	Concentration	Route	Fixed Doses
Powder 10 MIU (single dose)	10 MIU/mL	IM, SC	N/A
Solution 25 MIU multidose	10 MIU/mL	IM, SC	N/A

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

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

Dose: The recommended dose of INTRON A for the treatment of chronic hepatitis B is 3 million IU/m^2 three times a week (TIW) for the first week of therapy followed by dose escalation to 6 million IU/m^2 TIW (maximum of 10 million IU TIW) administered subcutaneously for a total duration of 16 to 24 weeks.

Dosage Forms for This Indication

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

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

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

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

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

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

PREPARATION AND ADMINISTRATION Reconstitution of INTRON® A Powder for Injection Reconstitute INTRON A Powder for Injection with 1 mL of Sterile Water for Injection, USP. The Sterile Water for Injection supplied contains 5 mL and is intended for single use. Discard the unused portion. 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.

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

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** and **Instructions for Use** for detailed instructions).

Please refer to the **MEDICATION GUIDE** and **Instructions for Use** 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** and **Instructions for Use** for detailed instructions).

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

- ***Intravenous Infusion***

The infusion solution should be prepared immediately prior to use. Based on the desired dose, the appropriate vial strength(s) of INTRON A should be reconstituted with the diluent provided. Inject 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 into a 100-mL bag of 0.9% Sodium Chloride Injection USP. The final concentration of INTRON A should not be less than 10 million IU/100 mL.

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

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

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

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

HOW SUPPLIED

INTRON® A Powder for Injection

INTRON A Powder for Injection, 10 million IU per vial and Diluent for INTRON A (Sterile Water for Injection USP) 5 mL per vial; boxes containing 1 INTRON A vial and 1 vial of INTRON A Diluent (NDC 0085-4350-01).

INTRON A Powder for Injection, 18 million IU per vial and Diluent for INTRON A (Sterile Water for Injection USP) 5 mL per vial; boxes containing 1 vial of INTRON A and 1 vial of INTRON A Diluent (NDC 0085-4351-01).

INTRON A Powder for Injection, 50 million IU per vial and Diluent for INTRON A (Sterile Water for Injection USP) 5 mL per vial; boxes containing 1 INTRON A vial and 1 vial of INTRON A Diluent (NDC 0085-4352-01).

INTRON A Solution for Injection in Vials

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

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

Storage

- **INTRON A Powder for Injection/Reconstitution**
  INTRON A Powder for Injection should be stored in the refrigerator at 2° to 8°C (36°-46°F). After reconstitution, the solution should be used immediately, but may be stored up to 24 hours at 2° to 8°C (36°-46°F). Throw away any medicine left in the vial after you withdraw 1 dose.
- **INTRON A Solution for Injection in Vials**
  INTRON A Solution for Injection in vials should be stored in the refrigerator at 2° to 8°C (36°-46°F).
  INTRON A Solution for Injection should not be frozen and should be kept away from heat. Throw away any unused INTRON A Solution for Injection remaining in the vial after one month.

References:

1. Smalley R, et al. *N Engl J Med.* 1992;327:1336-1341.
2. Aviles A, et al. *Leukemia and Lymphoma.* 1996;20:495-499.
3. Unterhalt M, et al. *Blood.* 1996;88(10 Suppl 1):1744A.
4. Schiller J, et al. *J Biol Response Mod.* 1989;8:252-261.

5. Poynard T, et al. *N Engl J Med.* 1995;332(22)1457-1462.

6. Lin R, et al. *J Hepatol.* 1995;23:487-496.

7. Perrillo R, et al. *N Engl J Med.* 1990;323:295-301.

8. Perez V, et al. *J Hepatol.* 1990;11:S113-S117.

9. Knodell R, et al. *Hepatology.* 1981;1:431-435.

10. Perrillo R, et al. *Ann Intern Med.* 1991;115:113-115.

11. Kauppila A, et al. *Int J Cancer.* 1982;29:291-294.

Manufactured by: Schering Corporation, a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889 USA.

For patent information: www.merck.com/product/patent/home.html

Copyright © 1986, 2011 Schering Corporation, a subsidiary of **Merck & Co., Inc.** All rights reserved.

Rev. 05/2015

uspi-mk2958-mtl-5ml-XXXXrXXX

MEDICATION GUIDE

INTRON® A (In-tron-aye)

(Interferon alfa-2b, recombinant)

Read this Medication Guide before you start taking INTRON A, and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

If you are taking INTRON A with REBETOL, also read the Medication Guide for REBETOL® (ribavirin) Capsules and Oral Solution.

INTRON A alone is a treatment for certain types of cancers and hepatitis B virus. INTRON A by itself or with REBETOL is a treatment for some people infected with hepatitis C virus.

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

INTRON A can cause serious side effects that:

- **may cause death, or**
- **may worsen certain serious diseases that you may already have.**

Tell your healthcare provider right away if you have any of the symptoms listed below while taking INTRON A. If symptoms get worse, or become severe and continue, your healthcare provider may tell you to stop taking INTRON A permanently. In many, but not all people, these symptoms go away after they stop taking INTRON A.

1. Heart problems. Some people who take INTRON A may develop heart problems, including:

- low blood pressure
- fast heart rate or abnormal heart beats
- trouble breathing or chest pain
- heart attacks or heart muscle problems (cardiomyopathy)

2. Stroke or symptoms of a stroke. Symptoms may include weakness, loss of coordination, and numbness. Stroke or symptoms of a stroke may happen in people who have some risk factors **or** no known risk factors for a stroke.

3. Mental health problems, including suicide. INTRON A may cause you to develop mood or behavior problems that may get worse during treatment with INTRON A or after your last dose, including:

- irritability (getting upset easily)
- depression (feeling low, feeling bad about yourself, or feeling hopeless)
- acting aggressive, being angry or violent
- thoughts of hurting yourself or others, or suicide
- former drug addicts may fall back into drug addiction or overdose

If you have these symptoms, your healthcare provider should carefully monitor you during treatment with INTRON A and for 6 months after your last dose.

4. **New or worsening autoimmune disease**. Some people taking INTRON A develop autoimmune diseases (a condition where the body's immune cells attack other cells or organs in the body), including rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, and psoriasis. In some people who already have an autoimmune disease, the disease may get worse while on INTRON A.

5. **Infections.** Some people who take INTRON A may get an infection. Symptoms may include:
   - fever
   - chills
   - bloody diarrhea
   - burning or pain with urination
   - urinating often
   - coughing up mucus (phlegm) that is discolored (for example yellow or pink)

While taking INTRON A, you should see a healthcare provider regularly for check-ups and blood tests to make sure that your treatment is working and to check for side effects.

What is INTRON A?

INTRON A is a prescription medicine that is used:

- to treat adults with a blood cancer called hairy cell leukemia
- to treat certain adults with a type of skin cancer called malignant melanoma
- to treat adults with some types of Follicular Non-Hodgkin's Lymphoma along with certain chemotherapy medicines
- to treat certain adults with genital warts (condylomata acuminate), by injecting the medicine directly into the warts
- to treat certain adults with a type of cancer caused by AIDS, called AIDS-related Kaposi's Sarcoma
- alone to treat adults with chronic (lasting a long time) hepatitis C infection with stable liver problems
- with REBETOL to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with stable liver problems
- to treat chronic (lasting a long time) hepatitis B infection in people 1 year and older with stable liver problems

Who should not take INTRON A?

Do not take INTRON A if you:

- had a serious allergic reaction to another alpha interferon product or are allergic to any of the ingredients in INTRON A. See the end of this Medication Guide for a complete list of ingredients. Ask your healthcare provider if you are not sure.
- have certain types of hepatitis (autoimmune hepatitis)
- have certain other liver problems

Talk to your healthcare provider before taking INTRON A if you have any of these conditions.

What should I tell my healthcare provider before taking INTRON A?

Before you take INTRON A, tell your healthcare provider if you:

- **See "What is the most important information I should know about INTRON A?"**
- have or ever had any problems with your heart, including heart attack or have high blood pressure
- have or ever had bleeding problems or blood clots
- are being treated for a mental illness or had treatment in the past for any mental illness, including depression and thoughts of hurting yourself or others
- have any kind of autoimmune disease (where the body's immune system attacks the body's own cells), such as psoriasis, systemic lupus erythematosus, rheumatoid arthritis
- have or ever had low blood cell counts
- have ever been addicted to drugs or alcohol
- have cirrhosis or other liver problems (other than hepatitis B or C)
- have or had lung problems, such as chronic obstructive pulmonary disease (COPD)
- have diabetes
- have colitis (inflammation of your intestine)
- have a condition that suppresses your immune system, such as cancer
- have hepatitis B or C infection
- have HIV infection (the virus that causes AIDS)
- have kidney problems
- have high blood triglyceride levels (fat in your blood)
- have an organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if INTRON A will harm your unborn baby. You should use effective birth control during treatment with INTRON A. Talk to your healthcare provider about birth control choices for you during treatment with INTRON A. Tell your healthcare provider if you become pregnant during treatment with INTRON A.
- are breast-feeding or plan to breast-feed. It is not known if INTRON A passes into your breast milk. You and your healthcare provider should decide if you will use INTRON A or breast-feed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. INTRON A and certain other medicines may affect each other and cause side effects.

Especially tell your healthcare provider if you take:

- the anti-hepatitis B medicine telbivudine (Tyzeka)
- the anti-HIV medicine zidovudine (Retrovir)
- theophylline (Theo-24, Elixophyllin, Uniphyl, Theolair). Your healthcare provider may need to monitor the amount of theophylline in your body and make changes to your theophylline dose.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take INTRON A?

- INTRON A is given as an injection under the skin (subcutaneous) or into a muscle (intramuscular), into genital lesions, or as an injection into a vein (intravenous), depending on the condition that is being treated.
- Your healthcare provider will decide your dose of INTRON A and how often you will take it.
- If your healthcare provider decides that you can inject INTRON A for your condition, inject it exactly as prescribed, under your skin (subcutaneous injection) or into your muscle (intramuscular injection). Do not change your dose or how you inject INTRON A unless your healthcare provider tells you to.
- Do not take more than your prescribed dose.
- Your healthcare provider should show you how to prepare and measure your dose of INTRON A and how to inject yourself before you use INTRON A for the first time.
- You should not inject INTRON A until your healthcare provider has shown you how to use INTRON A the right way.
- INTRON A comes as:
    - a powder for injection in a vial that is used only 1 time (single-use vial). The powder must be mixed with water for injection (a diluent) before you inject it.
    - a solution for injection in a multi-dose vial
- See the attached Instructions for Use for detailed instructions for preparing and injecting a dose of INTRON A.
- If you miss a dose of INTRON A, take the missed dose as soon as possible during the same day or the next day, then continue on your regular dosing schedule. If several days go by after you miss a dose, check with your healthcare provider to see what to do.

- Do not inject more than 1 dose or take more than your prescribed dose without talking to your healthcare provider.
- If you take too much INTRON A, call your healthcare provider right away. Your healthcare provider may examine you more closely, and do blood tests.
- Your healthcare provider should do blood tests before you start INTRON A, and regularly during your treatment to see how well the treatment is working and to check for side effects.

What are the possible side effects of INTRON A?

INTRON A may cause serious side effects including:

- **See "What is the most important information I should know about INTRON A?"**
- **Blood problems.** INTRON A can affect your bone marrow and cause low white blood cell and platelet counts. In some people, these blood counts may fall to dangerously low levels. If your blood cell counts become very low, you can get infections or have bleeding problems.
- **Serious eye problems.** INTRON A may cause eye problems that may lead to vision loss or blindness. You should have an eye exam before you start taking INTRON A. If you have eye problems or have had them in the past, you may need eye exams while taking INTRON A. Tell your healthcare provider or eye doctor right away if you have any vision changes while taking INTRON A.
- **Thyroid problems.** Some people develop changes in the function of their thyroid. Symptoms of thyroid problems include:
  - problems concentrating
  - feeling cold or hot all the time
  - changes in your weight
  - skin changes
- **Blood sugar problems**. Some people may develop high blood sugar or diabetes. If you have high blood sugar or diabetes before starting INTRON A, talk to your healthcare provider before you take INTRON A. If you develop high blood sugar or diabetes while taking INTRON A, your healthcare provider may tell you to stop INTRON A and prescribe a different medicine for you. Symptoms of high blood sugar or diabetes may include:
    - increased thirst
    - tiredness
    - urinating more often than normal
    - increased appetite
    - weight loss
    - your breath smells like fruit
- **Lung problems including:**
  - trouble breathing
  - pneumonia

- inflammation of lung tissue
- new or worse high blood pressure of the lungs (pulmonary hypertension). This can be severe and may lead to death.

You may need to have a chest X-ray or other tests if you develop fever, cough, shortness of breath, or other symptoms of a lung problem during treatment with INTRON A.

- **Severe liver problems, or worsening of liver problems including liver failure and death**. Symptoms may include:
  - nausea
  - loss of appetite
  - tiredness
  - diarrhea
  - yellowing of your skin or the white part of your eyes
  - bleeding more easily than normal
  - swelling of your stomach area (abdomen)
  - confusion
  - sleepiness
  - you cannot be awakened (coma)
- **Serious allergic reactions and skin reactions. Symptoms may include:**
  - itching
  - swelling of your face, eyes, lips, tongue, or throat
  - trouble breathing
  - anxiousness
  - chest pain
  - feeling faint
  - skin rash, hives, sores in your mouth, or your skin blisters and peels
- **Swelling of your pancreas (pancreatitis) and intestines (colitis).** Symptoms may include:
  - severe stomach area (abdomen) pain
  - severe back pain
  - nausea
  - vomiting
  - fever
- **New or worsening autoimmune disease**. Some patients taking INTRON A develop autoimmune diseases (a condition where the body's immune cells attack other cells or organs in the body), including rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, and psoriasis. In some patients who already have an autoimmune disease, the disease may worsen while on INTRON A.
- **Nerve problems.** People who take INTRON A or other alpha interferon products with telbivudine (Tyzeka) can develop nerve problems such as continuing numbness, tingling, or burning sensation in the arms or legs (peripheral neuropathy). Call your healthcare provider if you have any of these symptoms.
- **Growth problems in children.** Weight loss and slowed growth are common in children during combination treatment with INTRON A and REBETOL. Most children will go through a growth spurt and gain weight after treatment stops. Some children may not

reach the height that they were expected to have before treatment. Talk to your healthcare provider if you are concerned about your child's growth during treatment with INTRON A and REBETOL.

- **Dental and gum problems.**

Tell your healthcare provider right away if you have any of the symptoms listed above.

The most common side effects of INTRON A include:

- **Flu-like symptoms**. Symptoms may include: headache, muscle aches, tiredness, and fever. Some of these symptoms may be decreased by injecting your INTRON A dose in the evening. Talk to your healthcare provider about which over-the-counter medicines you can take to help prevent or decrease some of the symptoms.
- **Tiredness**. Many people become very tired during treatment with INTRON A.
- **Appetite problems.** Nausea, loss of appetite, and weight loss can happen with INTRON A.
- **Skin reactions**. Redness, swelling, and itching are common at the injection site.
- **Hair thinning**.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the side effects of INTRON A. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1–800–FDA–1088.

How should I store INTRON A?

INTRON A Solution for Injection:

- Store in the refrigerator between 36°F to 46°F (2°C to 8°C).
- INTRON A Solution for Injection in Multidose vials for injection may be used to give more than 1 injection of medicine.
- Do not freeze.
- Throw away any unused INTRON A Solution for Injection remaining in the vial after one month.

INTRON A Powder for Injection:

Before mixing, store in the refrigerator between 36°F to 46°F (2°C to 8°C).

- After mixing the INTRON A Powder for Injection, use the solution right away or store the solution in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Throw away any medicine left in the vial after you withdraw 1 dose.
- Do not freeze.

Keep INTRON A and all medicines out of the reach of children.

General Information about INTRON A

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use INTRON A for a condition for which it was not prescribed. Do not give INTRON A to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about INTRON A. If you would like more information, ask your healthcare provider. You can ask your healthcare provider or pharmacist for information about INTRON A that was written for health care professionals.

- For more information, go to www.IntronA.com or call 1-800-622-4477.

What are the ingredients in INTRON A?

Active ingredient: interferon alfa-2b

Inactive ingredients:

- **Powder for injection contains**: glycine, sodium phosphate dibasic, sodium phosphate monobasic, human albumin. Sterile water for injection is provided as a diluent.
- **Solution Multidose vials for injection contain**: sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, edetate disodium, polysorbate 80, and m-cresol as a preservative.

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

Manufactured by: Schering Corporation, a subsidiary of **Merck & Co., Inc.,** Whitehouse Station, NJ 08889 USA

Revised: 05/2015

Copyright © 1996, 2011 Schering Corporation, a subsidiary of **Merck & Co., Inc.**
All rights reserved.

usmg-mk2958-mtl-XXXXrXXX