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PRODUCT INFORMATION

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

WARNING

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

DESCRIPTION

INTRON A for intramuscular, subcutaneous, intralesional, or intravenous Injection is a purified sterile recombinant interferon product.

Interferon alfa-2b, recombinant for Injection has been classified as an alfa interferon and is a water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride at a concentration of 5 to 10 mg/L; the presence of this antibiotic is not detectable in the final product. The specific activity of Interferon alfa-2b, recombinant is approximately 2.6 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† Interferon alfa-2b, recombinant per vial	Route of Administration
10	1	10	0.038	IM, SC, IV, IL
18	1	18	0.069	IM, SC, IV
50	1	50	0.192	IM, SC, IV

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

† Based on the specific activity of approximately 2.6 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
10 MIU single dose	10 million IU/1.0 mL	0.038	SC, IL
18‡ MIU multidose	3 million IU/0.5 mL	0.088	IM, SC
25¶ MIU multidose	5 million IU/0.5 mL	0.123	IM, SC, IL

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

† Based on the specific activity of approximately 2.6 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 Interferon alfa-2b, recombinant for Injection (for a label strength of 18 million IU).

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

Solution in Multidose Pens for Injection

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

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

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

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 alfa 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 undetected by 16 hours after the injections.

After intravenous administration, serum INTRON A concentrations peaked (135 to 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 <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, pediatric and adults with detectable

serum neutralizing antibodies, the titers detected were low (22/24 with titers ≤1:40 and 2/24 with titers ≤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 ≥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 >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 ≤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 vs. observation patients was 1.72 years vs 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 vs 26% for observation patients. Median overall survival time for INTRON A treated patients vs observation patients was 3.82 years vs 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 vs 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% vs 41%; median RFS 2.4 vs 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 >7 cm; involvement of at least three nodal sites (each with a diameter of >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 6 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 vs 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 alfa to anthracycline-containing combination chemotherapy regimens,[1-3] the addition of interferon alfa 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 ≤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 vs 17% of placebo patients experienced clearing of all treated lesions. Likewise, 24% of INTRON A patients vs 8% of placebo patients experienced marked (≥75% to <100%) reduction in lesion size, 18% vs 9% experienced moderate (≥50% to ≤75%) reduction in lesion size, 10% vs 42% had a slight (<50%) reduction in lesion size, 5% vs 24% had no change in lesion size, and 0% vs 1% experienced exacerbation (p<0.001).

In one of these studies, 43% (54/125) of patients in whom multiple (≤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 Interferon alfa-2b, recombinant for Injection 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 posttreatment. 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 vs 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 vs 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 subcutaneously were 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 >200 (30.7 months) than in patients with CD4 ≤200 (8.9 months). Among responders, the median survival time was 22.6 months vs 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 vs 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 posttreatment 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 MIU 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 (<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 alfa interferon alone; pediatric patients previously untreated with alfa interferon experienced a sustained virologic response. See REBETOL package insert 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 vs 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 (≤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 posttreatment liver biopsies using the semi-quantitative 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] vs 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 <100 pg/mL were more likely to respond to INTRON A therapy than were patients with a baseline HBV DNA >100 pg/mL (35% vs 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% vs 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/m^2 TIW, SC and 35 million IU QD, SC			
	Asymptomatic		Symptomatic	
CD4<200	4/14	(29%)	0/19	(0%)

200≤CD4≤400	6/12	(50%)		0/5	(0%)
			} 58%		
CD4>400	5/7	(71%)		0/0	(0%)

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

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

Study Number	Treatment Group* - Number of Patients (%) 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.

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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 posttherapy.
† Patients pretreated with prednisone not shown.
‡ INTRON A treatment group vs untreated control.
§ Untreated control patients evaluated after 24-week observation period. A subgroup subsequently received INTRON A therapy. A direct comparison is not applicable (NA).

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TABLE 4
ALT RESPONSES* 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	16/38	(42%)	--	--	8/42	(19%)	0.03
2	--	--	10/24	(42%)	1/22	(5%)	0.0034
3	--	--	12/24‡	(50%)	2/27	(7%)‡	NA‡
All Studies	**16/38**	**(42%)**	**22/48**	**(46%)**	**11/91**	**(12%)**	--

* Reduction in serum ALT to normal by 6 months posttherapy.
† INTRON A treatment group vs untreated control.

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

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

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 ≤2 mg/dL

- Albumin — Stable and within normal limits
- Prothrombin Time — <3 seconds prolonged
- WBC — $\geq 3000/mm^3$
- Platelets — $\geq 70,000/mm^3$

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 (ribavirin, USP) is indicated for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alfa interferon therapy and in patients 18 years of age and older who have relapsed following alfa interferon therapy. See REBETOL package insert 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* <3 seconds prolonged

Pediatrics ≤2 seconds prolonged

- WBC ≥4000/mm^3
- Platelets *Adults* ≥100,000/mm^3

Pediatrics ≥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 Interferon alfa-2b, recombinant for Injection. 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 posttherapy, 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 posttreatment.

A transient increase in ALT ≥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 ≥3 mg/dL (≥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 alfa or any component of the product.
- Autoimmune hepatitis
- Decompensated liver disease

INTRON A and REBETOL (ribavirin, USP) 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)

See REBETOL package insert 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 (eg, chronic obstructive pulmonary disease), or diabetes mellitus prone to ketoacidosis. Caution should also be observed in patients with coagulation disorders (eg, 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 **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 Interferon alfa-2b, recombinant for Injection. Hypotension may occur during INTRON A administration, or up to 2 days posttherapy, 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.

Neuropsychiatric Disorders

DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL IDEATION, SUICIDAL ATTEMPTS, AND COMPLETED SUICIDES HAVE BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALFA INTERFERONS, INCLUDING INTRON A THERAPY. Patients with a preexisting psychiatric condition, especially depression, or a history of severe psychiatric disorder should not be treated with INTRON A.[11] INTRON A therapy should be discontinued for any patient developing severe depression or other 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. 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.

Bone marrow toxicity

INTRON A therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of 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 (<0.5 x 10^9/L) or platelet counts (<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 and papilledema 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 pre-existing ophthalmologic disorders (eg, 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 Interferon alfa-2b, recombinant for Injection 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 alfa treated patients, including those treated with INTRON A. Any patient developing liver function abnormalities during treatment should be monitored closely and if appropriate, treatment should be discontinued.

Pulmonary Disorders

Pulmonary infiltrates, pneumonitis and pneumonia, including fatality, have been observed in interferon alfa treated patients, including those treated with INTRON A. 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 alfa treatment should be discontinued. While this has been reported more often in patients with chronic hepatitis C treated with interferon alfa, it has also been reported in patients with oncologic diseases treated with interferon alfa.

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 alfa 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 alfa 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.

Use with Ribavirin (See also REBETOL Package Insert) 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 (ribavirin, USP) was associated with hemolytic anemia. Hemoglobin <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 (ribavirin, USP) should **not** be used in patients with creatinine clearance <50 mL/min. See REBETOL package insert for additional information.

PRECAUTIONS

General Acute serious hypersensitivity reactions (eg, 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 (eg, triglycerides >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 alfa 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, 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.
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

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, 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 Interferon alfa-2b, recombinant for Injection 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 (ribavirin, USP) should be used with caution in fertile men. See REBETOL package insert 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 (ribavirin, USP) (see **CONTRAINDICATIONS**). See REBETOL package insert for additional information. Significant teratogenic and/or embryocidal effects have been demonstrated in all animals species exposed to ribavirin. REBETOL therapy is contraindicated in women who are pregnant. See **CONTRAINDICATIONS** and the REBETOL package insert. If pregnancy occurs in a patient or partner of a

patient during treatment with INTRON A and REBETOL and during the 6 months after treatment cessation, physicians should report such cases by calling (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, DOSAGE AND ADMINISTRATION; Chronic Hepatitis B**).

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 package insert 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.

Geriatric Use In all clinical studies of INTRON A (Interferon alfa-2b, recombinant), 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 postmarking 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.

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

Treatment-Related Adverse Experiences By Indication

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

Treatment-Related Adverse Experiences By Indication

	Dosing Regimens Percentage (%) of Patients*									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C[‖]	CHRONIC HEPATITIS B		
								Adults		Pediatrics
	20 MIU/m^2 Induction (IV) 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
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
nausea	66	24	21	17	28	21	19	50	33	18
taste alteration	24	2	13	<1	5	7	2	10	--	--
abdominal pain	2	20	<5	1	5	21	16	5[†]	4	23
loose stools	--	1	--	<1	--	10	2	2	--	2
vomiting	[†]	32	6	2	11	14	8	7	10	27
constipation	1	14	<1	--	1	10	4	5	--	2
gingivitis	2[‡]	7[‡]	--	--	--	14	--	1	--	--
dyspepsia	--	2	--	2	4	--	7	3	8	3
other (<5%)	abdominal ascites, abdominal distension, colitis, dysphagia, eructation, esophagitis, flatulence, gallstones, gastric ulcer, gastritis, gastroenteritis, gastrointestinal disorder (7% in follicular lymphoma), gastrointestinal hemorrhage, gastrointestinal mucosal discoloration, gingival bleeding, gum hyperplasia, halitosis, hemorrhoids, increased appetite, increased saliva, intestinal disorder, melena, mouth ulceration, mucositis, oral hemorrhage, oral leukoplakia, rectal bleeding after stool, rectal hemorrhage, stomatitis, stomatitis ulcerative, taste loss, tongue disorder, tooth disorder									
Liver and Biliary System Disorders (<5%)	abnormal hepatic function tests, billary pain, bilirubinemia, hepatitis, increased lactate dehydrogenase, increased transaminases (SGOT/SGPT) (elevated SGOT 63% in malignant melanoma and 24% in follicular lymphoma), jaundice, right upper quadrant pain (15% in chronic hepatitis C), and very rarely, hepatic encephalopathy, hepatic failure, and death									
Musculoskeletal System Disorders										
musculoskeletal pain	--	18	--	--	--	--	21	9	1	10
Other (<5%)	arteritis, arthritis, arthritis aggravated, arthrosis, bone disorder, bone pain, carpal tunnel syndrome, hyporeflexia, leg cramps, muscle atrophy, muscle weakness, polyarteritis nodosa, tendinitis, rheumatoid arthritis, spondylitis									
Nervous System and Psychiatric Disorders										
depression	40	9	6	3	9	28	19	17	6	4
paresthesia	13	13	6	1	3	21	5	6	3	<1
impaired concentration	--	1	--	<1	3	14	3	8	5	3
amnesia	[§]	1	<5	--	--	14	--	--	--	--
confusion	8	2	<5	4	12	10	1	--	--	2
hypoesthesia	--	1	<5	1	--	10	--	--	--	--
irritability	1	1	--	--	--	--	13	16	12	22
somnolence	1	2	<5	3	3	--	33[¶]	14	9	5
anxiety	1	9	5	<1	1	3	5	2	--	3
insomnia	5	4	--	<1	3	3	12	11	6	8
nervousness	1	1	--	1	--	3	2	3	--	3
decreased libido	1	1	<5	--	--	--	1	5	1	--
other (<5%)	abnormal coordination, abnormal dreaming, abnormal gait, abnormal thinking, aggravated depression, aggressive reaction, agitation (7% in chronic hepatitis B pediatrics), alcohol intolerance, apathy, aphasia, ataxia, Bell's palsy, CNS dysfunction, coma, convulsions, delirium, dysphonia, emotional lability, extrapyramidal disorder, feeling of ebriety, flushing, hearing disorder, hearing impairment, hot flashes, hyperesthesia, hyperkinesia, hypertonia, hypokinesia, impaired consciousness, labyrinthine disorder, loss of consciousness, manic depression, manic reaction, migraine, neuralgia, neuritis, neuropathy, neurosis, paresis, paroniria, parosmia, personality disorder, polyneuropathy, psychosis, speech disorder, stroke, suicidal ideation, suicide attempt, syncope, tinnitus, tremor, twitching, vertigo (8% in follicular lymphoma)									
Reproduction System	amenorrhea (12% in follicular lymphoma), dysmenorrhea, impotence, leukorrhea, menorrhagia, menstrual irregularity, pelvic pain, penis disorder, sexual dysfunction, uterine bleeding, vaginal dryness									

Treatment-Related Adverse Experiences By Indication

	Dosing Regimens Percentage (%) of Patients*									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C‖	CHRONIC HEPATITIS B		
								Adults		Pediatrics
	20 MIU/m^2 Induction (IV) 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
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
Disorders (<5%)										
Resistance Mechanism Disorders										
moniliasis	--	1	--	<1	--	17	--	--	--	--
herpes simplex	1	2	--	1	--	3	1	5	--	--
other (<5%)	abscess, conjunctivitis, fungal infection, hemophilus, herpes zoster, infection, infection bacterial, infection nonspecific (7% 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, nontherapetic 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 >20% of INTRON A treated patients included neutropenia (92%), fever (81%), myalgia (75%), anorexia (69%), vomiting/nausea (66%), increased SGOT (63%), headache (62%), chills (54%), depression (40%), diarrhea (35%), alopecia (29%), altered taste sensation (24%), dizziness/vertigo (23%), and anemia (22%).

Adverse reactions classified as severe or life-threatening (ECOG Toxicity Criteria grade 3 or 4) were recorded in 66% and 14% of INTRON A treated patients, respectively. Severe adverse reactions recorded in >10% of INTRON A treated patients included neutropenia/leukopenia (26%), fatigue (23%), fever (18%), myalgia (17%), headache (17%), chills (16%), and increased SGOT (14%). Grade 4 fatigue was recorded in 4% and grade 4 depression was recorded in 2% of INTRON A treated patients. No other grade 4 AE was reported in more than 2 INTRON A treated patients. Lethal hepatotoxicity occurred in 2 INTRON A treated patients early in the clinical trial. No subsequent lethal 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 >5% of CHVP plus INTRON A treated patients included neutropenia (34%), asthenia (10%), and vomiting (10%). The incidence of neutropenic infection was 6% in CHVP plus INTRON A vs 2% in CHVP alone. One patient in each treatment group required hospitalization.

Twenty-eight percent of CHVP plus INTRON A treated patients had a temporary modification/interruption of their INTRON A therapy, but only 13 patients (10%) permanently stopped INTRON A therapy because of toxicity. There were 4 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 Interferon alfa-2b, recombinant for Injection for condylomata acuminata who were evaluable for safety, reported an adverse reaction during treatment. The incidence of the adverse reactions reported increased when the number of treated lesions increased from one to five. All 40 patients who had five warts treated, reported some type of adverse reaction during treatment.

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

AIDS-Related Kaposi's Sarcoma In patients with AIDS-Related Kaposi's Sarcoma, some type of adverse reaction occurred in 100% of the 74 patients treated with 30 million IU/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 Two studies of extended treatment (18 to 24 months) with INTRON A Interferon alfa-2b, recombinant for Injection show that approximately 95% of all patients treated experience some type of adverse event and that patients treated for extended duration continue to experience adverse events throughout treatment. Most adverse events reported are mild to moderate in severity. However, 29/152 (19%) of patients treated for 18 to 24 months experienced a serious adverse event compared to 11/163 (7%) of those treated for 6 months. Adverse events which occur or persist during extended treatment are similar in type and severity to those occurring during short-course therapy.

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

In patients using combination treatment with INTRON A and REBETOL (ribavirin, USP), 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 package insert for additional information.

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

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

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

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

Abnormal Laboratory Test Values by Indication

	Dosing Regimens Percentage (%) of Patients									
	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CONDYLOMATA ACUMINATA	AIDS-RELATED KAPOSI'S SARCOMA		CHRONIC HEPATITIS C	CHRONIC HEPATITIS B		
								Adults		Pediatrics
	20 MIU/m^2 Induction (IV) 10 MIU/m^2 Maintenance (SC)	5 MIU TIW/SC	2 MIU/m^2 TIW/SC	1 MIU/lesion	30 MIU/m^2 TIW/SC	35 MIU QD/SC	3 MIU TIW	5 MIU QD	10 MIU TIW	6 MIU/m^2 TIW
LABORATORY TESTS	N=143	N=135	N=145	N=352	N=69-73	N=26-28	N=140-171	N=96-101	N=75-103	N=113-115
Hemoglobin	22	8	NA	--	1	15	26[¶]	32[*]	23[*]	17[**]
White Blood Cell Count	[‖]	--	NA	17	10	22	26[†]	68[†]	34[†]	9[†]
Platelet Count	15	13	NA	--	0	8	15[‡]	12[‡]	5[‡]	1[‡]
Serum Creatinine	3	2	0	--	--	--	6	3	0	3
Alkaline Phosphatase	13	--	4	--	--	--	--	8	4	0
Lactate Dehydrogenase	1	--	0	--	--	--	--	--	--	--
Serum Urea Nitrogen	12	4	0	--	--	--	--	2	0	2
SGOT	63	24	4	12	11	41	--	--	--	--
SGPT	2	--	13	--	10	15	--	--	--	--
Granulocyte Count										
• Total	92	36	NA	--	31	39	45[§]	75[§]	61[§]	70[§]
• 1000-<1500/mm^3	66	--	--	--	--	--	32	30	32	43
• 750-<1000/mm^3	--	21	--	--	--	--	10	24	18	18
• 500-<750/mm^3	25	--	--	--	--	--	1	17	9	7
• <500/mm^3	1	13	--	--	--	--	2	4	2	2

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

* Decrease of ≥2 g/dL

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

† Decrease to <3000/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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

General

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

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

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

Hairy Cell Leukemia (see DOSAGE AND ADMINISTRATION, General)

Dose: The recommended dose for the treatment of hairy cell leukemia is 2 million IU/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 10 MIU (single dose)	10 MIU/mL	SC	N/A
Solution 18 MIU multidose	6 MIU/mL	IM, SC	N/A
Solution 25 MIU multidose	10 MIU/mL	IM, SC	N/A
Pen 3 MIU/dose multidose	15 MIU/mL	SC	1.5, 3.0, 4.5
Pen 5 MIU/dose multidose	25 MIU/mL	SC	2.5, 5.0

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 or Multidose Pens is NOT recommended for intravenous administration and should not be used for the induction phase of malignant melanoma.

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

Dose adjustment:

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

- INTRON A should be withheld for severe adverse reactions, including granulocyte counts >250mm^3 but <500mm^3 or SGPT/SGOT >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 <250mm^3 or SGPT/SGOT of >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 10 MIU	10 MIU/mL	SC	N/A
Solution 18 MIU multidose	6 MIU/mL	SC	N/A
Solution 25 MIU multidose	10 MIU/mL	SC	N/A
Pen 3 MIU/dose Multidose*	15 MIU/mL	SC	1.5, 3.0, 4.5, 6.0
Pen 5 MIU/dose Multidose	25 MIU/mL	SC	7.5, 10.0
Pen 10 MIU/dose Multidose	50 MIU/mL	SC	10.0, 15.0, 20.0

*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 >250mm^3 but <500mm^3 or SGPT/SGOT >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 <250mm^3 or SGPT/SGOT of >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 10 MIU (single dose)	10 MIU/mL	SC	N/A
Solution 18 MIU multidose	6 MIU/mL	SC	N/A
Solution 25 MIU multidose	10 MIU/mL	SC	N/A
Pen 5 MIU/dose multidose	25 MIU/mL	SC	2.5, 5.0
Pen 10 MIU/dose multidose	50 MIU/mL	SC	5.0

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

Dose adjustment:

- Doses of myelosuppressive drugs were reduced by 25% from a full-dose CHOP regimen, and cycle length increased by 33% (eg, from 21 to 28 days) when alfa interferon was added to the regimen.
- Delay chemotherapy cycle if neutrophil count was <1500/mm^3 or platelet count was <75, 000/mm^3
- INTRON A should be permanently discontinued if SGOT exceeds >5x the upper limit of normal or serum creatinine >2.0 mg/dl (see **WARNINGS**).
- Administration of INTRON A therapy should be withheld for a neutrophil count <1000/mm^3, or a platelet count <50,000/mm^3.
- INTRON A dose should be reduced by 50% (2.5 MIU TIW) for a neutrophil count >1000/mm^3, but <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 >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 12-16 weeks.

Dosage Forms for this Indication

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

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

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

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

Dose adjustment: None

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

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

Dose: The recommended dose of INTRON A for Kaposi's Sarcoma is 30 million IU/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 either in vials or in Multidose Pens should NOT be used for AIDS-Related Kaposi's Sarcoma.

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

Dose adjustment:

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

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

Dosage Forms for this Indication

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

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

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

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

Dosage Forms for this Indication

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

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 10 MIU (single dose)	10 MIU/mL	SC	N/A
Solution 25 MIU multidose	10 MIU/mL	SC	N/A
Pen 3 MIU/dose multidose	15 MIU/mL	SC	1.5, 3.0, 4.5, 6.0
Pen 5 MIU/dose multidose	25 MIU/mL	SC	2.5, 5.0, 7.5, 10.0
Pen 10 MIU/dose multidose	50 MIU/mL	SC	5.0, 10.0, 15.0, 20.0

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

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

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

- **Intravenous Infusion**

The infusion solution should be prepared immediately prior to use. Based on the desired dose, the appropriate vial strength(s) of INTRON A should be reconstituted with the diluent provided. Inject 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/100mL.

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

INTRON A Solution for Injection in Vials

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

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

The single-use 10 million IU vial is supplied with B-D Safety-Lok* syringes. The Safety-Lok* syringe contains a plastic safety sleeve to be pulled over the needle

after use. The syringe locks with an audible click when the green stripe on the safety sleeve covers the red stripe on the needle. The B-D Safety-Lok* syringes provided with the 10 MIU Solution for Injection cannot be used for IM injections.

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

Solution for Injection in Multidose Pens

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

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

HOW SUPPLIED

INTRON A Powder for Injection

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

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

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

INTRON A Solution for Injection in Multidose Pens

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

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

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

INTRON A Solution for Injection in Vials

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

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

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

Storage

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

- **INTRON A Solution for Injection in Vials**
  Intron A Solution for Injection in Vials should be stored at 2° to 8°C (36° to 46°F).

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

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 1/06 B-XXXXXXXXT

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

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MEDICATION GUIDE

INTRON® A
(Interferon alfa-2b, recombinant)

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

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

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

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

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

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

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

The most serious possible side effects of INTRON A include:

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

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

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

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

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

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

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

What is INTRON A?

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

It is not known if INTRON A or INTRON A/REBETOL combination therapy can cure hepatitis B or C (*permanently eliminate the virus*) or if it can prevent liver failure or liver cancer that is caused by hepatitis B or C infection.
It is also not known if INTRON A or INTRON A/REBETOL combination therapy will prevent one infected person from infecting another person with hepatitis B or C.

Who should not take INTRON A?

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

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

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

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

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

How should I take INTRON A?

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

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

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

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

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

What should I avoid while taking INTRON A?

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

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

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

What are the possible side effects of INTRON A?

Possible, serious side effects include:

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

Common but less serious side effects include:

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

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

General advice about prescription medicines

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

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

Manufactured by: Schering Corporation Kenilworth, NJ 07033 USA

Issued: 12/05

Instructional leaflet and video are available through your doctor.

*Novofine is a registered trademark of Novo Nordisk

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

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

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

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

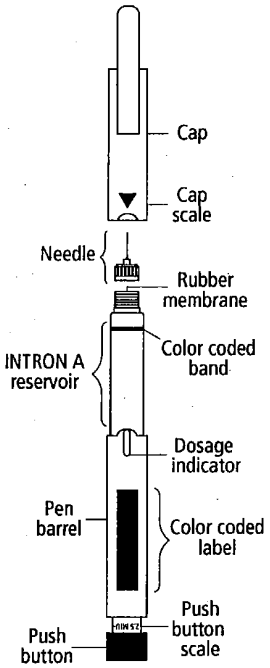
Make sure that you have the correct INTRON A multidose pen as prescribed by your healthcare provider.

Description of your INTRON A multidose pen

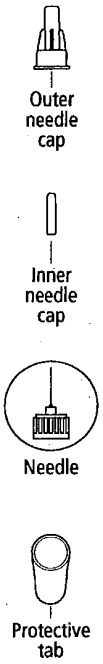
- The INTRON A multidose pen should **ONLY** be used with **Novofine*** needles. These are the needles that come packaged with the pen. If you use other needles, the pen may not work properly, and you could get the wrong dose of INTRON A.

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

INTRON A Pen



Novofine Needle Assembly



- The **color-coded push button** and **push button scale**. These are located at the bottom of the pen when it is held with the cap side up. This tells you the dose that has been set.
- The **color-coding** band. This is located on the INTRON A reservoir. The band lets you know the dose that you are using. The 3 MIU INTRON A multidose pen has a brown push button, a brown color-coding band and color-coded label. The 5 MIU INTRON A multidose pen has a light blue push button, a light blue color-coding band and color-coded label. The 10 MIU INTRON A multidose pen has a pink push button, a pink color-coding band and color-coded label.

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

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

Storing INTRON A Solution Multidose Pen for Injection

INTRON A Solution Multidose Pen for Injection should be stored in the refrigerator between 2° and 8°C (36° and 46°F). Discard any unused INTRON A pen remaining after 4 weeks. **DO NOT FREEZE**.

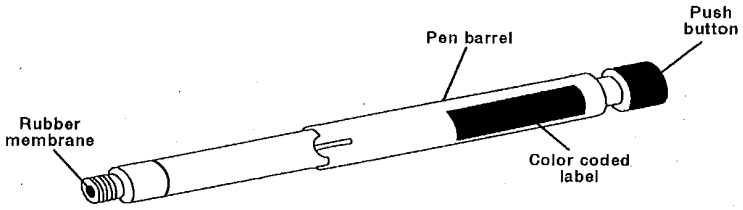
How do I prepare for an injection using the INTRON A multidose pen?

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

   - the Intron A Multidose Pen
   - two alcohol swabs
   - a cotton ball or gauze
   - a puncture-proof disposable container

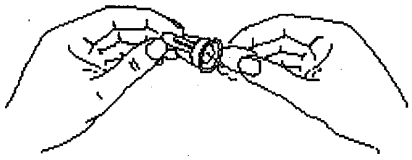
2. Before removing the Multidose Pen from the carton, check the date printed on the carton to make sure that the expiration date has not passed. Do not use if the expiration date has passed.

3. Wash your hands with soap and warm water. It is important to keep your work area, your hands, and injection site clean to minimize the risk of infection.
4. Remove the multidose pen from the carton. Pull the cap off the pen and wipe the rubber membrane with one alcohol swab.

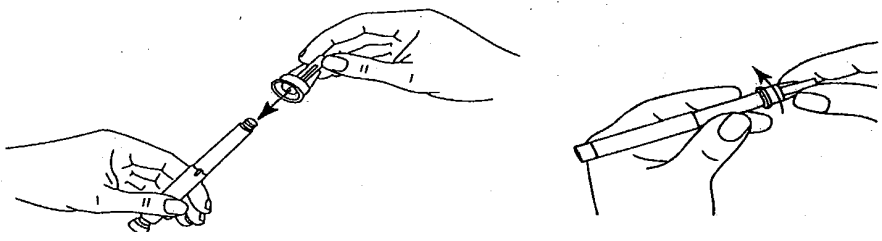


5. Check the solution inside the pen. The solution should be clear and colorless, without particles. Do not use the INTRON A if the medicine is cloudy, has particles, or is any color besides clear and colorless.

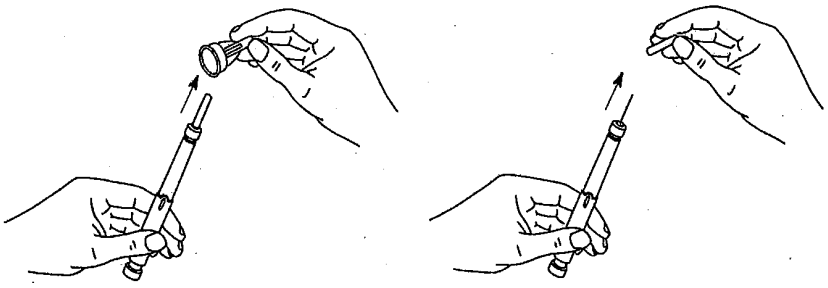
6. Remove the paper backing from the Novofine needle by pulling the paper tab. You will see the back of the needle once the paper tab is removed.



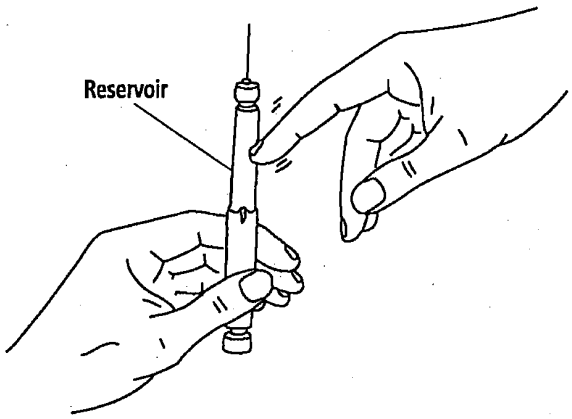
7. Keep the needle in its outer clear needle cap and gently push the Novofine needle straight into the pen's rubber membrane you just cleaned. Screw the needle onto the INTRON A multidose pen by turning it clockwise.



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

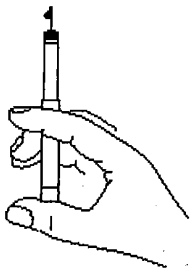


9. Keep the needle facing up and remove any air bubbles that may be in the reservoir by tapping the reservoir with your finger. If you have any air bubbles, they will rise to the top of the reservoir.

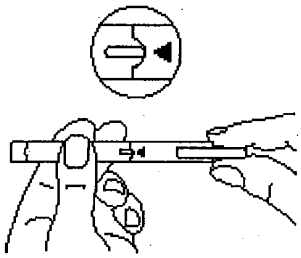


10. Hold the pen by the barrel and turn the INTRON A reservoir clockwise until you feel it click into place.

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

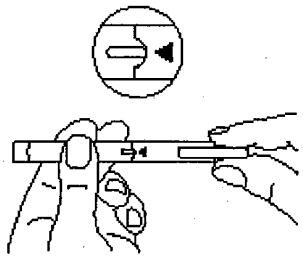


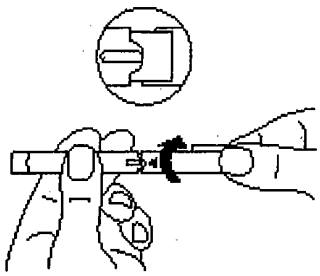
12. Place the cap back on the INTRON A multidose pen. Make sure you line up the black triangle on the pen cap with the dosage indicator on the pen barrel. The pen is now ready to set the dose.



Setting the dose prescribed by your doctor

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

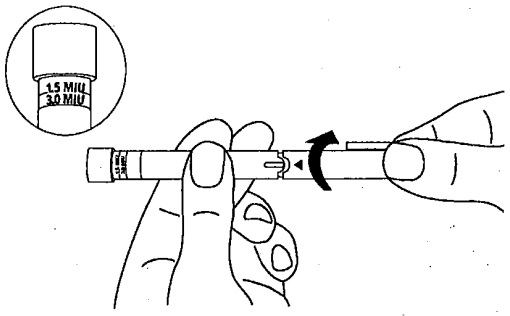




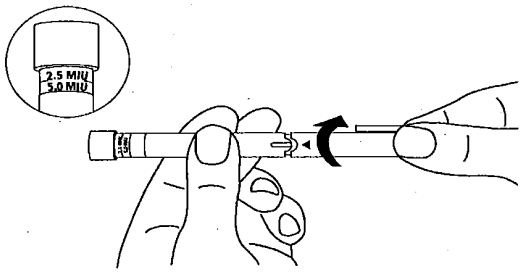
14. Set the dose prescribed by your healthcare provider by turning the cap clockwise. With each clockwise turn, the push button will rise and you will see

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

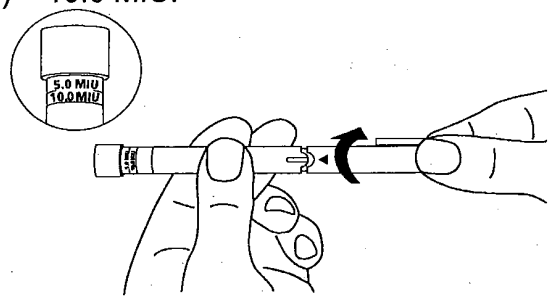
- To set a 3.0 MIU dose using the 3 MIU multidose pen, turn the cap 2 full turns (10 clicks) = 3.0 MIU.



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



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



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

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

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

1 full turn (5 clicks) = 1.5 MIU
3 full turns (15 clicks) = 4.5 MIU

4 full turns (20 clicks) = 6.0 MIU

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

1 full turn (5 clicks) = 2.5 MIU
3 full turns (15 clicks) = 7.5 MIU
4 full turns (20 clicks) = 10.0 MIU

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

1 full turn (5 clicks) = 5.0 MIU
3 full turns (15 clicks) = 15.0 MIU
4 full turns (20 clicks) = 20.0 MIU

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

17. If you have set a wrong dose, turn the cap back (counterclockwise) as far as you can until the push button is all the way in and the push button scale is completely covered, then begin at step 12 again.

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

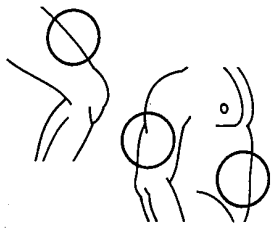
19. Place the multidose pen on your flat work surface until you are ready to inject INTRON A.

Choosing an injection site

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

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

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



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

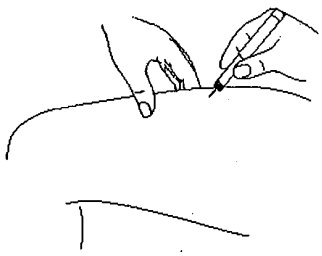
Injecting your dose of INTRON A

1. Clean the injection site with a new alcohol swab.

2. Pick up the multidose pen from your flat work surface and remove the cap from the needle.

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

4. With the other hand, hold the multidose pen (like a pencil) at a **45 degree angle** to the skin. Use a quick "dart-like" motion to push the needle into the skin.



5. After the needle is in, remove the hand used to pinch the skin and use it to hold the pen barrel. If blood comes into the pen reservoir, the needle has entered a blood vessel. **Do not inject INTRON A.** Withdraw the needle and discard the used multidose pen in the puncture-proof container. Contact your healthcare provider. Repeat the steps to prepare for an injection.

6. If no blood is present in the pen reservoir, inject the medicine by gently pressing the push button all the way down.

7. Leave the needle in place for a few seconds while holding down the push button.

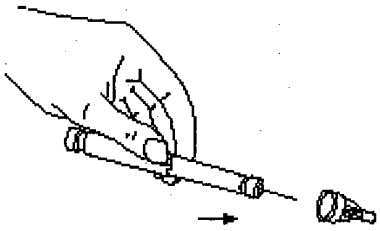
8. Slowly release the push button and pull the needle out of the skin.

9. Place a cotton ball or gauze over the injection site and press for several seconds. Do not massage the injection site. If there is bleeding, cover the injection site with a bandage.

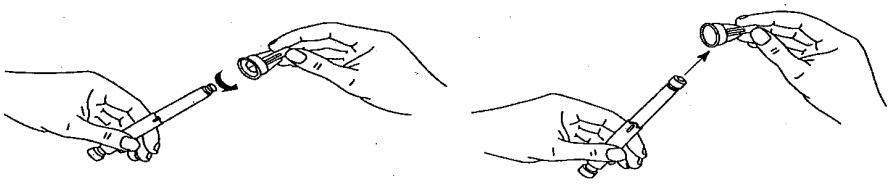
10. It is important to check your injection site approximately two hours after your injection for redness, swelling, or tenderness. These are signs of inflammation that you may need to talk to your healthcare provider about if they do not go away.

Removing the needle from the multidose pen

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

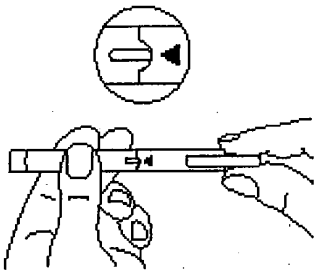


12. Once capped, remove the needle by holding the clear outer needle cap with one hand and holding the pen barrel with the other hand, turning counterclockwise.



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

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



Storing INTRON A Solution Multidose Pen for Injection

INTRON A Solution Multidose Pen for Injection should be stored in the refrigerator between 2° and 8°C (36° and 46°F). **DO NOT FREEZE**. Discard any unused INTRON A pen remaining after 4 weeks.

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

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

- The needles should never be reused.

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

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

- **Always keep the container out of the reach of children.**

*Novofine is a registered trademark of Novo Nordisk

Schering Corporation
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U.S. Patent Nos. 5,766,582; 5,935,566; 6,610,830
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