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F-24937623

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

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PRODUCT INFORMATION

WARNING

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 Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy.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

DESCRIPTION

INTRON A Interferon alfa-2b, recombinant 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 2.6×10^8 IU/mg protein as measured by the HPLC assay.

Powder for Injection

Vial Strength	mL Diluent	Final Concentration after Reconstitution million IU/mL*	mg INTRON A† Interferon alfa-2b, recombinant	Route of Administration
5 MIU	1	5	0.019	IM, SC, IV
10 MIU	2	5	0.038	IM, SC, IV, IL++
18 MIU	1	18	0.069	IM, SC, IV
25 MIU	5	5	0.096	IM, SC, IV
50 MIU	1	50	0.192	IM, SC, IV

*Each mL also contains 20 mg glycine, 2.3 mg sodium phosphate dibasic, 0.55 mg sodium phosphate monobasic, and 1.0 mg human albumin.
†Based on the specific activity of approximately 2.6×10^8 IU/mg protein, as measured by HPLC assay.
++The 10 MIU vial for intralesional use should be reconstituted with 1 mL of the provided diluent.

Prior to administration, the INTRON A Powder for Injection is to be reconstituted with the provided Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) containing 0.9% benzyl alcohol as a preservative (see **DOSAGE AND ADMINISTRATION**) INTRON A Powder for Injection is a white to cream-colored powder.

Solution Vials for Injection

Vial Strength	Final Concentration*	mg INTRON A† Interferon alfa-2b, recombinant	Route of Administration
3 MIU	3 million IU/0.5 mL	0.012	IM, SC
5 MIU	5 million IU/0.5 mL	0.019	IM, SC, IL
10 MIU	10 million IU/1.0 mL	0.038	IM, SC, IL
18‡ MIU multidose	3 million IU/0.5 mL	0.088	IM, SC
25¶ MIU multidose	5 million IU/0.5 mL	0.123	IM, SC, IL

*Each mL contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.
†Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay.
‡This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b, recombinant per 3.8 mL in order to provide the delivery of six 0.5-mL doses, each containing 3 million IU of INTRON A Interferon alfa-2b, recombinant for Injection (for a label strength of 18 million IU).
¶This is a multidose vial which contains a total of 32.0 million IU of interferon alfa-2b, recombinant per 3.2 mL in order to provide the delivery of five 0.5-mL doses, each containing 5 million IU of INTRON A Interferon alfa-2b, recombinant for Injection (for a label strength of 25 million IU).

Solution in Multidose Pens for Injection

Pen Strength	Final Concentration*	INTRON A Dose Delivered (6 doses, 0.2 mL each)	mg INTRON A†	Route of Administration
18 MIU	22.5 MIU/1.5 mL	3 MIU/dose	0.087	SC
30 MIU	37.5 MIU/1.5 mL	5 MIU/dose	0.144	SC
60 MIU	75 MIU/1.5 mL	10 MIU/dose	0.288	SC

*Each mL also contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.
†Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay.

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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection following both intramuscular and subcutaneous injections was approximately 2 to 3 hours. Serum concentrations were undetectable by 16 hours after the injections.

After intravenous administration, serum INTRON A concentrations peaked (135 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 non-splenectomized 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 Interferon alfa-2b, recombinant for Injection was evaluated as adjuvant to surgical treatment in patients with melanoma who were free of disease (postsurgery) 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). 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 six cycles administered every 2 months for 1 year. Patients in both treatment groups received a total of 12 CHVP cycles over 18 months.

The group receiving the combination of INTRON A therapy plus CHVP had a significantly longer progression-free survival (2.9 years 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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 were subcutaneously similar and are provided together in TABLE 1. This table demonstrates the relationship of response to baseline CD4 count in both asymptomatic and symptomatic patients in the 30 million IU/m^2 TIW and the 35 million IU/QD treatment groups.

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

For patients who received 30 million IU TIW, the median survival time was longer in patients with CD4 >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 Interferon alfa-2b, recombinant for Injection 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 million IU TIW subcutaneously for 96 weeks. In both studies, patient follow-up was variable and some data collection was retrospective.

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

A subset (<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.

REBETRON® Combination Therapy containing INTRON A and REBETOL® (ribavirin, USP) Capsules has been shown to provide a significant reduction in virologic load and improved histologic response in patients with compensated liver disease who have relapsed following therapy with alfa interferon alone and in patients previously untreated with alfa interferon. See REBETRON Combination Therapy package insert for additional information.

Chronic Hepatitis B *Adults* The safety and efficacy of INTRON A Interferon alfa-2b, recombinant for Injection 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) have 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 semiquantitative Knodell Histology Activity Index.[9] No statistically significant difference in liver histology was observed in treated patients compared to control patients in Study 1. Although statistically significant histological improvement from baseline was observed in treated patients in Study 3 (p≤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 Interferon alfa-2b, recombinant for Injection 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 maxiumum 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.

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

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

*Intent to treat groups.
† Study 1: 72 weeks of treatment; Study 2: 96 weeks of treatment.
‡ Confidence intervals adjusted for multiple comparisons due to 3 treatment arms in the study.

TABLE 3
VIROLOGIC RESPONSE IN **CHRONIC HEPATITIS B** PATIENTS*
Treatment Group†— Number of Patients (%)

Study Number	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).

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

Study Number	INTRON A 5 million IU QD	INTRON A 10 million IU TIW	Untreated Controls	P† Value
1	16/38 (42%)	— —	8/42 (19%)	0.03
2	— —	10/24 (42%)	1/22 (5%)	0.0034
3	— —	12/24‡ (50%)	2/27 (7%)‡	NA‡
All Studies	**16/38 (42%)**	**22/48 (46%)**	**11/91 (12%)**	**—**

*Reduction in serum ALT to normal by 6 months 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 Interferon alfa-2b, recombinant for Injection is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia.

Malignant Melanoma INTRON A Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 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 ≥3000/mm^3
- Platelets ≥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) Capsules is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alfa interferon therapy or who have relapsed following alfa interferon therapy. See REBETRON Combination Therapy package insert for additional information.

Chronic Hepatitis B INTRON A Interferon alfa-2b, recombinant for Injection 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 x 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 INTRON A responders (*adults* 63%, 24/38; *pediatrics

hepatitis B. The 5 million, 18 million, and 25 million IU strengths of the INTRON A Powder for Injection are not to be used for the intralesional treatment of condylomata acuminata since the dilution required for the intralesional use would result in a hypertonic solution.

The INTRON A multidose pens, the 3 million IU vial, and the 18 million IU multidose vial of INTRON A Solution for Injection are not to be used for the treatment of condylomata acuminata. The INTRON A multidose pens and the 18 million and 25 million IU multidose vials of INTRON A Solution for Injection are not to be used for the treatment of AIDS-Related Kaposi's Sarcoma. INTRON A Solution for Injection is not recommended for the intravenous treatment of malignant melanoma.

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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection. 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.

INTRON A Interferon alfa-2b, recombinant Powder for Injection when reconstituted with the provided Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) contains benzyl alcohol. There have been rare reports of death in infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in infants is not known. INTRON A **Powder for Injection** is not indicated for use in infants and should not be used in pediatric patients in this age group.

REBETRON Combination Therapy containing INTRON A and REBETOL (ribavirin, USP) Capsules was associated with hemolytic anemia. Hemoglobin <10 g/dL was observed in approximately 10% of patients in clinical trials. Anemia occurred within 1 to 2 weeks of initiation of ribavirin therapy. REBETRON Combination Therapy containing INTRON A and REBETOL is not recommended in patients with severe renal impairment and should be used with caution in patients with moderate renal impairment. See REBETRON Combination Therapy 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 Interferon alfa-2b, recombinant for Injection, 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 Interferon alfa-2b, recombinant for Injection 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 treatment should be directed in its appropriate use, informed of benefits and risks associated with treatment, and referred to the **PATIENT INFORMATION SHEET**. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. The full container should be disposed of according to the directions provided by the physician (see **PATIENT INFORMATION SHEET**).

Patients should be cautioned not to change brands of interferon without medical consultation as a change in dosage may result.

Patients receiving high INTRON A doses should be cautioned against performing tasks that would require complete mental alertness, such as operating machinery or driving a motor vehicle.

The most common adverse experiences occurring with INTRON A therapy are "flu-like" symptoms, such as fever, headache, fatigue, anorexia, nausea, or vomiting (see **ADVERSE REACTIONS**) and appear to decrease in severity as treatment continues. Some of these "flu-like" symptoms may be minimized by bedtime administration. Antipyretics may be used to prevent or partially alleviate the fever and headache. Another common adverse experience is thinning of the hair.

It is advised that patients be well hydrated, especially during the initial stages of treatment.

INTRON A in combination with REBETOL (ribavirin, USP) Capsules therapy must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of patients taking INTRON A/REBETOL therapy. Combination INTRON A/REBETOL therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. See REBETRON Combination Therapy package insert for additional information.

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 Interferon alfa-2b, recombinant for Injection (see **ADVERSE REACTIONS**); therefore, the monitoring of these laboratory parameters should be considered.

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility Studies with INTRON A Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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 Interferon alfa-2b, recombinant for Injection 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) Capsules should be used with caution in fertile men. See the REBETRON Combination Therapy package insert for additional information.

Pregnancy Category C INTRON A Interferon alfa-2b, recombinant for Injection 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 the REBETRON Combination Therapy containing INTRON A and REBETOL (ribavirin, USP) Capsules (see **CONTRAINDICATIONS**). See REBETRON Combination Therapy package insert for additional information.

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 below the age of 18 years have not been established for indications other than chronic hepatitis B.

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**). Safety and effectiveness in pediatric patients below the age of 1 year have not been established.

INTRON A Interferon alfa-2b, recombinant **Powder for Injection** when reconstituted with the provided Diluent for INTRON A Interferon alfa-2b, recombinant for Injection (bacteriostatic water for injection) contains benzyl alcohol and is not indicated for use in infants. There have been rare reports of death in infants associated with excessive exposure to benzyl alcohol. The amount of benzyl alcohol at which toxicity or adverse effects may occur in infants is not known (see **WARNINGS Chronic Hepatitis B**).

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 postmarketing reports for various indications, cardiovascular adverse events and confusion were reported more frequently in elderly patients receiving INTRON A therapy compared to younger patients.

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

ADVERSE REACTIONS

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

The most frequently reported adverse reactions were "flu-like" symptoms, particularly fever, headache, chills, myalgia, and fatigue. More severe toxicities are observed generally at higher doses and may be difficult for patients to tolerate. In addition, the following spontaneous adverse experiences have been reported during the marketing surveillance of INTRON A Interferon alfa-2b, recombinant for Injection: nephrotic syndrome, pancreatitis, psychosis, including hallucinations, renal failure, and renal insufficiency. Very rarely, INTRON A used alone or in combination with REBETOL (ribavirin, USP) Capsules 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 20 MIU/m² Induction (IV) 10 MIU/m² Maintenance (SC)	Follicular Lymphoma 5 MIU TIW/SC	Hairy Cell Leukemia 2 MIU/m² TIW/SC	Condylomata Acuminata 1 MIU/lesion	AIDS-Related Kaposi's Sarcoma 30 MIU/m² TIW/SC	AIDS-Related Kaposi's Sarcoma 35 MIU QD/SC	Chronic Hepatitis C‖ 3 MIU TIW	Chronic Hepatitis B Adults 5 MIU QD	Chronic Hepatitis B Adults 10 MIU TIW	Chronic Hepatitis B Pediatrics 6 MIU/m² TIW
ADVERSE EXPERIENCE	N=143	N=135	N=145	N=352	N=74	N=29	N=183	N=101	N=78	N=116
Application-Site Disorders			20							
injection site inflammation	—	1	—	—	—	—	5	3	—	—
other (≤5%)	burning, injection site bleeding, injection site pain, injection site reaction (5% in chronic hepatitis B pediatrics), itching									
Blood Disorders (<5%)	anemia, anemia hypochromic, granulocytopenia, hemolytic anemia, leukopenia, lymphocytosis, neutropenia (9% in chronic hepatitis C, 14% in chronic hepatitis B pediatrics), thrombocytopenia (10% in chronic hepatitis C) (bleeding 8% in malignant melanoma), thrombocytopenic purpura									
Body as a Whole										
facial edema	—	1	—	<1	—	10	<1	3	1	<1
weight decrease	3	13	<1	<1	5	3	10	2	5	3
other (≤5%)	allergic reaction, cachexia, dehydration, earache, hernia, edema, hypercalcemia, hyperglycemia, hypothermia, inflammation nonspecific, lymphadenitis, lymphadenopathy, mastitis, periorbital edema, poor peripheral circulation, peripheral edema (6% in follicular lymphoma), phlebitis superficial, scrotal/penile edema, thirst, weakness, weight increase									
Cardiovascular System Disorders (<5%)	angina, arrhythmia, atrial fibrillation, bradycardia, cardiac failure, cardiomegaly, cardiomyopathy, coronary artery disorder, extrasystoles, heart valve disorder, hematoma, hypertension (9% in chronic hepatitis C), hypotension, palpitations, phlebitis, postural hypotension, pulmonary embolism, Raynaud's disease, tachycardia, thrombosis, varicose vein									
Endocrine System Disorders (<5%)	aggravation of diabetes mellitus, goiter, gynecomastia, hyperglycemia, hyperthyroidism, hypertriglyceridemia, hypothyroidism, virilism									
Flu-like Symptoms										
fever	81	56	68	56	47	55	34	66	86	94
headache	62	21	39	47	36	21	43	61	44	57
chills	54	—	46	45	—	—	—	—	—	—
myalgia	75	16	39	44	34	28	43	59	40	27
fatigue	96	8	61	18	84	48	23	75	69	71
increased sweating	6	13	8	2	4	21	4	1	1	3
asthenia	—	63	7	—	11	—	40	5	15	5
rigors	2	7	—	—	30	14	16	38	42	30
arthralgia	6	8	8	9	—	3	16	19	8	15
dizziness	23	—	12	9	7	24	9	13	10	8
influenza-like symptoms	10	18	37	—	45	79	26	5	—	<1
back pain	—	15	19	6	1	3	—	—	—	—
dry mouth	1	2	19	—	22	28	5	6	5	—
chest pain	2	8	<1	<1	1	28	4	4	—	—
malaise	6	—	—	14	5	—	13	9	6	3
pain (unspecified)	15	9	18	3	3	3	—	—	—	—
other (<5%)	chest pain substernal, hyperthermia, rhinitis, rhinorrhea									
Gastrointestinal System Disorders										
diarrhea	35	19	18	2	18	45	13	19	8	12
anorexia	69	21	19	1	38	41	14	43	53	43
nausea	66	24	21	17	28	21	19	50	33	18
taste alteration	24	2	13	<1	5	7	2	10	—	—
abdominal pain	2	20	<5	1	5	21	16	5	4	23
loose stools	—	1	—	<1	—	10	2	2	—	2
vomiting	†	32	6	2	11	14	8	7	10	27
constipation	1	14	<1	—	1	10	4	5	—	2
gingivitis	2‡	7‡	—	—	—	14	—	1	—	—
dyspepsia	—	2	—	2	4	—	7	3	8	3
other (<5%)	abdominal ascites, abdominal distension, colitis, dysphagia, eructation, esophagitis, flatulence, gallstones, gastric ulcer, gastritis, gastroenteritis, gastrointestinal disorder (7% in follicular lymphoma), gastrointestinal hemorrhage, gastrointestinal mucosal discoloration, gingival bleeding, gum hyperplasia, halitosis, hemorrhoids, increased appetite, increased saliva, intestinal disorder, melena, mouth ulceration, mucositis, oral hemorrhage, oral leukoplakia, rectal bleeding after stool, rectal hemorrhage, stomatitis, stomatitis ulcerative, taste loss, tongue disorder, tooth disorder									
Liver and Biliary System Disorders (<5%)	abnormal hepatic function tests, biliary pain, bilirubinemia, hepatitis, increased lactate dehydrogenase, increased transaminases (SGOT/SGPT) (elevated SGOT 63% in malignant melanoma and 24% in follicular lymphoma), jaundice, right upper quadrant pain (15% in chronic hepatitis C), and very rarely, hepatic encephalopathy, hepatic failure, and death									
Musculoskeletal System Disorders										
musculoskeletal pain	—	18	—	—	—	—	21	9	1	10
other (<5%)	arteritis, arthritis, arthritis aggravated, arthrosis, bone disorder, bone pain, carpal tunnel syndrome, hyporeflexia, leg cramps, muscle atrophy, muscle weakness, polyarteritis nodosa, tendinitis, rheumatoid arthritis, spondylitis									
Nervous System and Psychiatric Disorders										
depression	40	9	6	3	9	28	19	17	6	4
paresthesia	13	13	6	1	3	21	5	6	3	<1
impaired concentration	—	1	—	<1	3	14	3	8	5	3
amnesia	§	1	<5	—	—	14	—	—	—	—
confusion	8	2	<5	4	12	10	1	—	—	2
hypoesthesia	—	1	<5	1	—	10	—	—	—	—
irritability	1	1	—	—	—	—	13	16	12	22
somnolence	1	2	<5	3	3	—	33¶	14	9	5
anxiety	1	9	5	<1	1	3	5	2	—	3
insomnia	5	4	—	<1	3	3	12	11	6	8
nervousness	1	1	—	1	—	3	2	3	—	3
decreased libido	1	1	<5	—	—	—	1	5	1	—
other (<5%)	abnormal coordination, abnormal dreaming, abnormal gait, abnormal thinking, aggravated depression, aggressive reaction, agitation (7% in chronic hepatitis B pediatrics), alcohol intolerance, apathy, aphasia, ataxia, Bell's palsy, CNS dysfunction, coma, convulsions, delirium, dysphonia, emotional lability, extrapyramidal disorder, feeling of ebriety, flushing, hearing disorder, hearing impairment, hot flashes, hyperesthesia, hyperkinesia, hypertonia, hypokinesia, impaired consciousness, labyrinthine disorder, loss of consciousness, manic depression, manic reaction, migraine, neuralgia, neuritis, neuropathy, neurosis, paresis, paroniria, parosmia, personality disorder, polyneuropathy, psychosis, speech disorder, stroke, suicidal ideation, suicide attempt, syncope, tinnitus, tremor, twitching, vertigo (8% in follicular lymphoma)									
Reproduction System Disorders (<5%)	amenorrhea (12% in follicular lymphoma), dysmenorrhea, impotence, leukorrhea, menorrhagia, menstrual irregularity, pelvic pain, penis disorder, sexual dysfunction, uterine bleeding, vaginal dryness									
Resistance Mechanism Disorders										
moniliasis	—	1	—	<1	—	17	—	—	—	—
herpes simplex	1	2	—	1	—	3	1	5	—	—
other (<5%)	abscess, conjunctivitis, fungal infection, hemophilus, herpes zoster, infection, infection bacterial, infection nonspecific (7% in follicular lymphoma), infection parasitic, otitis media, sepsis, stye, trichomonas, upper respiratory tract infection, viral infection (7% in chronic hepatitis C)									
Respiratory System Disorders										
dyspnea	15	14	<1	—	1	34	3	5	—	—
coughing	6	13	<1	—	—	31	1	4	—	5
pharyngitis	2	8	<5	1	1	31	3	7	1	7
sinusitis	1	4	—	—	—	21	2	—	—	—
nonproductive coughing	2	7	—	—	—	14	0	1	—	—
nasal congestion	1	7	—	1	—	10	<1	4	—	—
other (≤5%)	asthma, bronchitis (10% in follicular lymphoma), bronchospasm, cyanosis, epistaxis (7% in chronic hepatitis B pediatrics), hemoptysis, hypoventilation, laryngitis, lung fibrosis, pleural effusion, orthopnea, pleural pain, pneumonia, pneumonitis, pneumothorax, rales, respiratory disorder, respiratory insufficiency, sneezing, tonsillitis, tracheitis, wheezing									
Skin and Appendages Disorders										
dermatitis	1	—	8	—	—	—	2	1	—	—
alopecia	29	23	8	—	12	31	28	26	38	17
pruritus	—	10	11	1	7	—	9	6	4	3
rash	19	13	25	—	9	10	5	8	1	5
dry skin	1	3	9	—	9	10	4	3	—	<1
other (<5%)	abnormal hair texture, acne, cellulitis, cyanosis of the hand, cold and clammy skin, dermatitis lichenoides, eczema, epidermal necrolysis, erythema, erythema nodosum, folliculitis, furunculosis, increased hair growth, lacrimal gland disorder, lacrimation, lipoma, maculopapular rash, melanosis, nail disorders, nonherpetic cold sores, pallor, peripheral ischemia, photosensitivity, pruritus genital, psoriasis, psoriasis aggravated, purpura (5% in chronic hepatitis C), rash erythematous, sebaceous cyst, skin depigmentation, skin discoloration, skin nodule, urticaria, vitiligo									
Urinary System Disorders (<5%)	albumin/protein in urine, cystitis, dysuria, hematuria, incontinence, increased BUN, micturition disorder, micturition frequency, nocturia, polyuria (10% in follicular lymphoma), renal insufficiency, urinary tract infection (5% in chronic hepatitis C)									
Vision Disorders (<5%)	abnormal vision, blurred vision, diplopia, dry eyes, eye pain, nystagmus, photophobia									

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

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

Malignant Melanoma The INTRON A dose was modified because of adverse events in 65% (n=93) of the patients. INTRON A therapy was discontinued because of adverse events in 8% of the patients during induction and 18% of the patients during maintenance. The most frequently reported adverse reaction was fatigue which was observed in 96% of patients. Other adverse reactions that were recorded in >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 four deaths on study; two patients committed suicide in the CHVP plus INTRON A arm and two patients in the CHVP arm had unwitnessed sudden death. Three patients with hepatitis B (one of whom also had alcoholic cirrhosis) developed hepatotoxicity leading to discontinuation of INTRON A. Other reasons for discontinuation included intolerable asthenia (5/135), severe flu symptoms (2/135), and one patient each with exacerbation of ankylosing spondylitis, psychosis, and decreased ejection fraction.

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

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

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

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

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

In patients using REBETRON Combination Therapy containing INTRON A and REBETOL (ribavirin, USP) Capsules, the primary toxicity observed was hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of therapy. Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients treated with INTRON A/REBETOL therapy. See REBETRON Combination Therapy package insert for additional information.

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.

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 20 MIU/m² Induction (IV) 10 MIU/m² Maintenance (SC)	Follicular Lymphoma 5 MIU TIW/SC	Hairy Cell Leukemia 2 MIU/m² TIW/SC	Condylomata Acuminata 1 MIU/lesion	AIDS-Related Kaposi's Sarcoma 30 MIU/m² TIW/SC	AIDS-Related Kaposi's Sarcoma 35 MIU QD/SC	Chronic Hepatitis C 3 MIU TIW	Chronic Hepatitis B Adults 5 MIU QD	Chronic Hepatitis B Adults 10 MIU TIW	Chronic Hepatitis B Pediatrics 6 MIU/m² 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/mm³	66	—	—	—	—	—	32	30	32	43
• 750-<1000/mm³	—	21	—	—	—	—	10	24	18	18
• 500-<750/mm³	25	—	—	—	—	—	1	17	9	7
• <500/mm³	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%≥3g/dL
†Decrease to <3000/mm³
‡Decrease to <70,000/mm³
§Neutrophils plus bands
‖White Blood Cell Count was reported as neutropenia
¶Decrease of ≥2 g/dL; 20% 2-<3 g/dL; 6% ≥ 3 g/dL

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 overdosage 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.

HOW SUPPLIED

INTRON A Interferon alfa-2b, recombinant Powder for Injection INTRON A Interferon alfa-2b, recombinant Powder for