PDR®

46 EDITION

1992

PHYSICIANS' DESK REFERENCE®

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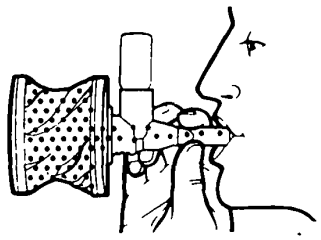
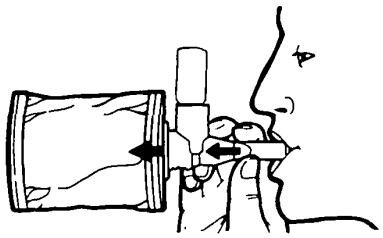
5. Breathe in *slowly* through the mouthpiece. If you hear a whistling sound, breathe slower until no sound can be heard.



6. Breathe in the entire contents of the bag. You will know to stop when the bag collapses and you cannot breathe in anymore.
7. *Hold his or her breath while slowly counting to five.*
8. Breathe out slowly into the bag.



9 Repeat the inhale/exhale cycle (steps 5 through 8) a second time, keeping lips tightly closed around the mouthpiece.

IMPORTANT NOTE: Repeat steps 2 through 9 for each dose of medication prescribed by your doctor.

10. Remove the mouthpiece from mouth. Take drug canister off the reservoir bag. Unlock mouthpiece from the bag and store all components in carrying case.

IMPORTANT CLEANING INSTRUCTIONS

Your patients should:

1. Clean only the mouthpiece thoroughly with warm (not hot) running water *at least* once a day. *InspirEase® is not dishwasher safe. Always clean by hand.*
2. The clear plastic reed section of the mouthpiece should not be touched due to potential breakage. We recommend a visual inspection of the reed section for signs of breakage prior to each use. If reed breakage occurs, replace mouthpiece immediately; otherwise replace mouthpiece as needed every six months.
3. After cleaning, wait until mouthpiece is *completely dry* before storing in carrying case. Do not place near artificial heat such as dishwasher or oven.
4. We recommend that the reservoir bag be replaced every two to three weeks or as needed. *However, if there is a hole or tear in it, replace immediately.*

NOTE: You will need a doctor's prescription for replacement bags or a new starter kit.

InspirEase is designed for use with most "spray inhaler" (metered dose inhaler) containers currently available; for single-patient use and single-dose use.

The usual caution should be exercised in dosing medications and evaluating patient response.

The prescribing information for the marketed MDIs varies with respect to dosing, administration, etc. We recommend that these be followed when using InspirEase.

CAUTION: Federal law restricts this device to sale by or on the order of a physician.

Rev. 3/89

REFERENCES

1. Sackner MA, Brown LK, Kim CS: *Chest* 80 (suppl): 915–918, 1981. 2. Tobin MJ, Jenouri G, Danta I, et al: *Am Rev Respir Dis* 126:670–675, 1982. 3. Saunders KB:*Br Med J* 1:1037–1038, 1965. 4. Gayrard P, Orehek J: *Respiration* 40:47–52, 1980. 5. Shim C, Williams MH Jr: *Am J Med* 69:891–894, 1980.

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INTRON® A

Interferon alfa-2b recombinant
For Injection

℞

DESCRIPTION

INTRON A Interferon alfa-2b, recombinant for intramuscular, subcutaneous or intralesional Injection is a purified sterile, lyophilized recombinant interferon formulation. The 3 million, 5 million, 25 million and 50 million IU packages are for use by intramuscular or subcutaneous injection. The 10 million IU package is for intramuscular, subcutaneous, or intralesional injection. (See **WARNINGS** and **PRECAUTIONS**.)

Interferon alfa-2b, recombinant 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 2×10^8 IU/mg protein.

The content of Interferon alfa-2b, recombinant is expressed in terms of International Units (IU). International Units are determined by comparison of the antiviral activity of the interferon alfa-2b, recombinant with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organization (WHO).

Each vial of INTRON A contains either 3 million, 5 million, 10 million, 25 million or 50 million IU of interferon alfa-2b, recombinant, 20 mg glycine, 2.3 mg sodium phosphate dibasic, 0.55 mg sodium phosphate monobasic, and 1.0 mg human albumin are also present. Based on the specific activity of INTRON A as approximately 2×10^8 IU/mg protein, the corresponding mg quantities of interferon alfa-2b, recombinant in the vials described above are approximately 0.015 mg, 0.025 mg, 0.05 mg, 0.125 mg, and 0.25 mg protein, respectively. Prior to administration, the lyophilized powder is to be reconstituted with the provided Diluent for INTRON A Interferon alfa-2b, recombinant (bacteriostatic water for injection) containing 0.9% benzyl alcohol as a preservative. (See **DOSAGE AND ADMINISTRATION**.)

Lyophilized INTRON A is a white to cream colored powder.

CLINICAL PHARMACOLOGY

General The interferons are a family of naturally occurring, small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or to various synthetic and biological inducers. Three major classes of interferons have been identified: alpha, beta, and gamma. These three classes are not homogenous, and each may contain several different molecular species of interferon. As an example, at least 14 genetically distinct human alpha interferons have been identified thus far. INTRON A has been classified as an alpha interferon.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Preliminary studies to characterize these membrane receptors and to determine the subsequent fate of the human interferon-receptor complex have been carried out using ^{125}I-labeled interferon alfa-2b, recombinant. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric membrane proteins. They exhibit selectivity for human but not murine interferons, suggesting species-specificity. Studies with other interferons have demonstrated varying degrees of species-specificity.

The results of several studies suggest that once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation, and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any of these activities might contribute to interferon's therapeutic effects.

Preclinical Pharmacology INTRON A Interferon alfa-2b, recombinant for Injection has exhibited antiproliferative effects in preclinical studies employing both cell culture systems and human tumor xenografts in animals, and has demonstrated significant immunomodulatory activity *in vitro*. The clinical significance of these findings is unknown.

The antiproliferative activity of INTRON A was evaluated *in vitro* using mouse and human leukemia cell lines, and human osteosarcoma, melanoma, and normal amnion cells. No activity was seen in mouse leukemia cells, which again suggests species-specificity.

The immunomodulating activity of INTRON A was demonstrated *in vitro* by its augmentation of the spontaneous "natural killer" activity of human lymphocytes, its enhancement of the tumoricidal activity of human monocytes against human tumor cells, and its induction of Class I histocompatibility antigens on the surface of a number of cell types. These effects appear to be dose-dependent.

In vivo studies of INTRON A showed inhibition of tumor growth. INTRON A injected *intralesionally* (0.2 million or 0.8 million IU once daily for 7 days) delayed the development and reduced the volume of human osteosarcoma implants in athymic mice. The effect was dose-related. Additionally, *subcutaneous* administration of INTRON A at a dose of 0.2 million IU/day inhibited the growth of implanted human breast tumor xenografts in athymic mice by about 50% after 23 days. INTRON A has not been shown to be effective in the treatment of osteosarcoma or carcinoma of the breast in humans.

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 cross-over design. INTRON A concentrations were determined using a radioimmunoassay (RIA) with a detection limit equal to 10 IU/mL.

The mean serum concentration of INTRON A 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-lives of INTRON A following both intramuscular and subcutaneous injections were approximately two to three hours. Serum concentrations were below the detection limit by 16 hours after the injections.

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

Urine concentrations of INTRON A 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 is no pharmacokinetic data available for the intralesional route of administration.

Hairy Cell Leukemia In clinical trials in patients with hairy cell leukemia, there was depression of circulating red blood cells, white blood cells and platelets during the first one to two months of treatment with INTRON A. Subsequently, both splenectomized and non-splenectomized patients with hairy cell leukemia, treated with INTRON A 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%. For the entire study group median plátelet counts were within the normal range after 2 months, median hemoglobin levels were in the normal range after 4 months and median granulocyte counts were in the normal range after 5 months of treatment. Responses of blood cell elements were similar in splenectomized and non-splenectomized patients except that median platelet counts after maximum response was to a level of 100,000/mm^3 in the latter group.

Treatment with INTRON A Interferon alfa-2b, recombinant for Injection resulted in a decrease in bone marrow hypercellularity and hairy cell infiltrates. The hairy cell index (HCI), which represents the percent of bone marrow cellularity times the percent of hairy cell infiltrate, was greater than or equal to 50% at the beginning of the study in 87% of patients. The percentage of patients with such an HCI decreased to 25% after six months and to 14% after one year. These results indicate that even though hematologic improvement had occurred earlier, prolonged treatment with INTRON A 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 with INTRON A. Additionally, the percentage of patients with confirmed and serious infections declined during treatment with INTRON A as granulocyte counts improved.

The responses observed in non-splenectomized patients included reversal of splenomegaly and of abnormalities in blood cell counts attributable to hypersplenism. In some cases there was reversal of clinically significant hypersplenism that may have resulted in need for splenectomy.

Reduced risk of major complications of hairy cell leukemia (serious infections, bleeding diatheses, transfusion requirements) were apparent within 3 months of initiation of treat-

Continued on next page

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ment in comparisons of INTRON A treated patients to a control group. No deaths occurred in patients treated with INTRON A during the subsequent 9 months of treatment and follow-up, while the mortality rate in the control group was 20% in the same time interval based on probability of survival analysis.

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%.

During the initial 3 months of treatment, there may be interferon-mediated suppression of hematopoiesis.

Serum Neutralizing Antibodies In a multicenter controlled clinical trial involving 145 hairy cell leukemia patients, no serum neutralizing antibodies were detected in the 90 patients evaluated.

In AIDS-Related Kaposi's Sarcoma patients treated with INTRON A, one out of 24 patients have developed detectable serum neutralizing antibodies.

Serum neutralizing antibodies have been detected in less than 3% of patients treated with higher doses of INTRON A in malignancies other than hairy cell leukemia or AIDS-Related Kaposi's Sarcoma. The clinical significance of these findings is unknown.

Condylomata Acuminata Condylomata acuminata (venereal or genital warts) are associated with infections of the human papilloma virus (HPV), especially HPV type-6 and possibly type-11. Given the antiviral and antiproliferative activities of interferons and the viral etiology of condylomata, placebo-controlled clinical trials were conducted to evaluate the efficacy and safety of intralesional injections of INTRON A in the treatment of condylomata acuminata

In the three controlled double-blind clinical trials conducted to determine the efficacy of INTRON A in condyloma, a total of 192 patients were evaluable for efficacy (a total of 224 were evaluable for safety). These patients were injected intralesionally with 1 million IU of INTRON A per lesion. Up to five lesions per patient were treated three times a week for three weeks, and the patients were then observed for up to 16 weeks after the full treatment course. These studies showed that INTRON A was significantly more effective than placebo in the treatment of condylomata, as measured by disappearance of lesions, decreases in lesion size, and by an overall change in disease status. In the 192 patients evaluated, 42% experienced clearing of all treated lesions, while 24% experienced marked (≥75% to <100%) and 18% experienced moderate (≥50% to <75%) reduction in lesion size, and 10% of patients had a slight reduction (<50%) in lesion size. Therefore, in these studies, 84% of patients experienced either lesion clearing or marked to moderate reduction in lesion size. INTRON A was effective in treating lesions of all sizes.

In one of these studies involving 125 patients in whom multiple (up to three) lesions were treated, a significant number of patients whose lesions were treated with INTRON A (54 patients out of 125 or 43%) experienced complete clearing of all treated lesions at one time or another during the course of the study. Of these 54 patients, 81% remained cleared of all treated lesions 16 weeks after treatment was initiated.

In this study, the percentage of patients who had one, two or three lesions treated and had all respective treated lesions cleared after one course of therapy ranged from 31 to 56%. Those 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. Overall percentage of patients who had all their treated lesions clear after two courses of treatment ranged from 57 to 85%.

Also from the above study, the INTRON A Interferon alfa-2b, recombinant for Injection treated lesions showed improvement within two to four weeks after the start of treatment. In 64% (68 patients out of 107) of those patients who experienced lesion clearing, or marked (≥75% to <100%) or moderate (≥50% to <75%) reduction in lesion size, the maximal response to INTRON A therapy was noted four to eight weeks after initiation of treatment. Additionally, a greater number of placebo-treated patients experienced exacerbations of their lesions during the posttreatment period, than did patients treated with INTRON A.

There was no significant difference in the clearing of lesions between those patients who had received other prior therapies for condylomata and those who had not. However, patients having condylomata for a shorter duration had better responses to treatment with INTRON A than those with lesions of a longer duration There was no difference in response to treatment of penile, vulvar or perianal condylomata or of condylomata appearing in heavily or lightly keratinized areas.

Serum neutralizing activity was detected in 0.8% of patients (2 out of 260) evaluated who received INTRON A intralesionally. The significance of the appearance of serum neutralizing activity is not known.

AIDS-Related Kaposi's Sarcoma Kaposi's Sarcoma (KS) is a common manifestation of the Acquired Immune Deficiency Syndrome (AIDS). Kaposi's Sarcoma lesions are usually cutaneous but may also occur throughout the gastrointestinal tract and occasionally affect visceral organs. They frequently are very numerous and may be painful and disfiguring.

INTRON A was administered to AIDS-Related Kaposi's Sarcoma patients in three separate clinical trials to evaluate efficacy and safety. A total of 144 patients were treated in these studies

The first clinical trial was a randomized study comparing the efficacy and safety of subcutaneous low dose (1 million IU/m^2 INTRON A) versus intravenous high dose (50 million IU/m^2 INTRON A) therapy. Both treatments were administered daily for 5 days every other week. Preliminary results showed objective responses in both regimens, but a shorter time to response and a higher response rate occurred with the 50 million IU/m^2 regimen. This study showed significantly greater activity in patients who were asymptomatic (afebrile and without weight loss) than in those with systemic symptoms (57% vs. 23%).

In the second clinical study patients with AIDS-Related KS received 30 million IU/m^2 of INTRON A, subcutaneously three times per week (TIW). Doses were adjusted for patient tolerance. In this study the average weekly dose delivered in the first four weeks was 150 million IU; at the end of twelve weeks this averaged 110 million IU/week; and by twenty-four weeks averaged 75 million IU/week. A response rate of 44% was obtained in asymptomatic patients versus 7% in symptomatic patients. The median time to response was approximately 2 months and the median duration of response was approximately three months for the asymptomatic patients. For the symptomatic patients, the median time to response was one month and median duration of response was also one month. Baseline T4/T8 ratios were 0.46 for responders vs. 0.33 for non-responders.

In a third study INTRON A was administered daily as a subcutaneous injection of 35 million IU/d for 12 weeks. Maintenance treatment, with every other day dosing, was continued for up to one year in patients achieving antitumor and antiviral responses. The median time to response was 2 months and median duration of response 5 months in the asymptomatic patients.

In all studies, the likelihood of response has been greatest in patients with relatively intact immune systems as assessed by baseline T4 counts (interchangeable with CD4) or T4/T8 ratios. Results at doses of 30 million IU/m^2 TIW and 35 million IU/daily, subcutaneously were similar and are provided together in Tables 1 and 2 below. These tables demonstrate the relationship of response to baseline T4 count or T4/T8 ratio in both asymptomatic (subtype A) and symptomatic (subtype B) patients in the 30 million IU/m^2 TIW dose and the 35 million IU/d dose.

TABLE 1
*RESPONSE BY BASELINE T4 COUNT**
30 million IU/m^2 TIW, SC and 35 million IU Daily, SC

	Asymptomatic		*Symptomatic*
T4 ≤ 200	4/14 (29%)		0/19 (0%)
200 ≤ T4 ≤ 400	6/12 (50%)	58%	0/5 (0%)
T4 > 400	5/7 (71%)		0/0 (0%)

TABLE 2
*RESPONSE BY T4/T8 RATIOS**
30 million IU/m^2 TIW, SC and 35 million IU Daily, SC

	Asymptomatic		*Symptomatic*
T4/T8 ≤ 0.25	1/13 (8%)		0/21 (0%)
0.25 ≤ T4/T8 ≤ 0.50	13/21 (62%)	60%	3/14 (21%)
0.50 ≤ T4/T8	11/19 (58%)		0/3 (0%)

* Data for T4, T4/T8, and asymptomatic and symptomatic classification was not available for all patients.

In the 30 million IU study group, there were 7% (5/72) of patients who 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) of the patients were partial responders.

For patients who received 30 million IU, TIW, the median survival time is longer in patients with T4 greater than 200 (30.7 months) than in patients with T4 less than or equal to 200 (8.9 months). Among responders, the median survival time was 22.6 months versus 9.7 months in non-responders.

Chronic Hepatitis Non-A, Non-B/C (NANB/C) The safety and efficacy of INTRON A Interferon alfa-2b, recombinant for Injection in the treatment of chronic hepatitis NANB/C was evaluated in four randomized controlled clinical studies in which INTRON A was administered subcutaneously at doses of 1, 2, or 3 million IU three times a week (TIW) for 6 months (23 or 24 weeks). All patients studied were 18 years of age or older and had compensated liver disease. Of the 332 patients evaluable for efficacy in these trials, 81% had a history of blood or blood product exposure, 8% had a history of intravenous drug abuse, 2% had a history of surgery without blood products, and the remainder had other exposure. Retrospectively, 86% (172/199) of the patients with blood or blood product exposure who were tested were found to be positive for antibody to hepatitis C virus (HCV).

In each of these four clinical studies, INTRON A was shown to produce a statistically significant improvement in serum alanine aminotransferase (ALT) levels. Three of the four studies used the 3 million IU dose of INTRON A, and gave the following results:

ALT RESPONSES‡
IN CHRONIC HEPATITIS NANB/C PATIENTS
Treatment Group
Number of Patients (%)

Study Number	*INTRON A 3 million IU*		*Controls**		*P† Value*
1[1]	29/55	(53%)	5/55	(9%)	<0.001
2	10/23	(43%)	3/25	(12%)	0.02
3	12/17	(71%)	3/17	(18%)	0.005
All Studies	**51/95**	**(54%)**	**11/97**	**(11%)**	**<0.001**

‡ Includes reduction in ALT level to:
normal,
near normal (≤1.5 times the upper limit of normal), or
partial response (>50% decrease in ALT level).
* Untreated or Placebo
† INTRON A 3 million IU, TIW, 6 months *versus* control.

Of the 54% of patients responding to INTRON A at a dose of 3 million IU, 70% achieved reductions in ALT levels to normal, 18% achieved reductions to near normal levels, and 12% achieved partial responses.

Histological improvement was evaluated by comparison of pre- and posttreatment liver biopsies using a pathologist's Global Assessment and the semi-quantitative Knodell Histology Activity Index (HAI).[2]

In one of the three studies there was a statistically significant histological improvement, as assessed by both methods, for patients treated with 3 million IU INTRON A Interferon alfa-2b, recombinant for Injection, compared to controls. A similar trend was observed in the two other studies; however the improvement was not statistically significant.

HISTOLOGICAL IMPROVEMENT
IN CHRONIC HEPATITIS NANB/C PATIENTS
A. Global Assessment
Treatment Group
Number of Patients (%)

Study Number	*INTRON A 3 million IU*		*Controls**		*P† Value*
1	23/45	(51%)	12/36	(33%)	0.12
2	11/18	(61%)	10/18	(56%)	1.00
3	14/16	(88%)	7/16	(44%)	0.02
All Studies	**48/79**	**(61%)**	**29/70**	**(41%)**	**0.01**

* Untreated or Placebo
† INTRON A 3 million IU, TIW, 6 months compared to control for improvement *versus* no improvement.

B. Knodell Histology Activity Index‡
Treatment Group
Number of Patients (%)

Study Number	*INTRON A 3 million IU*		*Controls**		*P† Value*
1	29/45	(64%)	18/36	(50%)	0.26
2	12/19	(63%)	10/18	(56%)	0.75
3	14/16	(88%)	8/15	(53%)	0.054
All Studies	**55/80**	**(69%)**	**36/69**	**(52%)**	**0.04**

‡ Includes the following:
Category I— Periportal necrosis
Category II— Intralobular degeneration and necrosis
Category III— Portal inflammation
Category IV— Fibrosis
* Untreated or Placebo
† INTRON A 3 million IU, TIW, 6 months compared to control for improvement *versus* no improvement.

Subsequent combined analysis of results for three studies, showed a statistically significant histological improvement in patients treated with INTRON A 3 million IU, compared to controls for both Global Assessment and the Knodell HAI. The improvement was due primarily to decreases in severity of necrosis and degeneration in the lobular and periportal regions (Knodell HAI Categories I + II), which were observed in 65% (52/80) of patients treated with 3 million IU INTRON A, compared to 46% (32/70) of controls. Diminution of disease activity in these regions of the liver was accompanied by a reduction or normalization of serum ALT level in many patients. Disease activity increased in these regions in only 3% of all patients treated with INTRON A at 3 million IU, whereas an increase was observed in 16% of the controls. No patient achieving an ALT response with 3 million IU INTRON A therapy showed increased periportal or lobular necrosis and degeneration.

Patients were followed for six months after the end of INTRON A therapy. During this period the ALT response was maintained in 51% (26/51) of patients who responded at the 3 million IU TIW dose. Of patients who relapsed during

the follow-up period and were retreated at this dose, 83% (15/18) responded to retreatment.

Serum Neutralizing Antibodies Serum anti-interferon neutralizing antibodies were detected in 15% (7/46) of the patients who received INTRON A for chronic hepatitis NANB/C at 3 million IU TIW for 6 months and were tested for antibody activity. The titers were low and the significance of the appearance of serum anti-interferon neutralizing activity is not known.

INDICATIONS AND USAGE

General INTRON A is indicated for the treatment of hairy cell leukemia, selected cases of condylomata acuminata involving external surfaces of the genital and perianal areas, AIDS-Related Kaposi's Sarcoma in select patients 18 years or older, and chronic hepatitis Non-A, Non-B/C (NANB/C) in patients 18 years of older with compensated liver disease who have a history of blood or blood product exposure and/or are HCV antibody positive.

Hairy Cell Leukemia *INTRON A for Injection is indicated* for the treatment of patients 18 years of age or older with hairy cell leukemia. Studies have shown that INTRON A can produce clinically meaningful regression or stabilization of this disease, both in previously splenectomized and non-splenectomized patients.

Prior to initiation of therapy, tests should be performed to quantitate peripheral blood hemoglobin, platelets, granulocytes and hairy cells and bone marrow hairy cells. These parameters should be monitored periodically during treatment to determine whether response to treatment has occurred. If a patient does not respond within 6 months, treatment should be discontinued. If a response to treatment does occur, treatment usually should be continued until no further improvement is observed and these laboratory parameters have been stable for about 3 months (see **DOSAGE AND ADMINISTRATION**). It is not known whether continued treatment after that time point is beneficial. Studies are in progress to evaluate this question.

The 50 million IU strength is not to be used for the treatment of hairy cell leukemia.

Condylomata Acuminata INTRON A Interferon alfa-2b, recombinant for Injection is indicated also for intralesional treatment of selected cases of condylomata acuminata involving external surfaces of the genital and perianal areas (see **DOSAGE AND ADMINISTRATION**). The 3 million, 5 million, and 25 million IU strengths are not to be used for the intralesional treatment of condylomata since the dilution required for intralesional use would result in a hypertonic solution. The 50 million IU strength is not to be used for the treatment of condylomata.

In selecting patients for treatment with INTRON A, the physician should consider the nature of the patient's lesion and the patient's past treatment history, in addition to the patient's ability to comply with the treatment regimen. INTRON A offers an additional approach to treatment in condyloma and is particularly useful for those patients who do not respond satisfactorily to other treatment modalities (e.g., podophyllin resin, surgery, cryotherapy, chemotherapy, and laser therapy), or whose lesions are more readily treatable by INTRON A than by other treatments.

The use of this product in adolescents has not been studied. Interferon alpha has been shown to affect the menstrual cycle and decrease serum estradiol and progesterone levels in females. Consideration should be given as to whether the adolescent patient should be treated.

AIDS-Related Kaposi's Sarcoma INTRON A is also indicated for the treatment of select patients, above 18 years of age with AIDS-Related Kaposi's Sarcoma. Studies have demonstrated a greater likelihood of response to INTRON A therapy in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system.

Lesion measurements and blood counts should be performed prior to initiation of therapy and should be monitored periodically during treatment to determine whether response to treatment or disease stabilization has occurred.

When disease stabilization or a response to treatment occurs, treatment should continue until there is no further evidence of tumor or until discontinuation is required by evidence of a severe opportunistic infection or adverse effect.

Chronic Hepatitis Non-A, Non-B/C (NANB/C) INTRON A is indicated for the treatment of chronic hepatitis Non-A, Non-B/C (NANB/C) in patients 18 years 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 can produce clinically meaningful effects on this disease, manifested by normalization of serum alanine aminotransferase (ALT) level 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 with no evidence of hepatic failure. Serum albumin and serum creatinine should be normal or near normal. Serum bilirubin should not exceed 2 mg/dL.

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. ALT levels should be evaluated after 2, 16, and 24 weeks of therapy to assess response to treatment.

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.

CONTRAINDICATIONS

INTRON A is contraindicated in patients with a history of hypersensitivity to interferon alfa or any component of the injection.

WARNINGS

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of therapy with INTRON A Interferon alfa-2b, recombinant for Injection.

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 cardiovascular disease (e.g., unstable angina, uncontrolled congestive heart failure), pulmonary disease (e.g., chronic obstructive pulmonary disease), or diabetes mellitus prone to ketoacidosis. Caution should also be observed in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Hairy Cell Leukemia Patients with platelet counts of less than 50,000/mm^3 should not be administered INTRON A intramuscularly, but instead by subcutaneous administration. The 50 million IU strength is not to be used for the treatment of hairy cell leukemia.

Cardiovascular adverse experiences, which include significant hypotension, arrhythmia, or tachycardia of 150 beats per minute or greater, were observed in approximately 3% of the patients studied who had various malignancies and were treated at doses higher than those for hairy cell leukemia. Transient reversible cardiomyopathy was reported in approximately 2% of the AIDS-Related Kaposi's Sarcoma patients treated with INTRON A Injection. Cardiomyopathy has also been reported in AIDS patients not receiving INTRON A therapy. The incidence of these complications in patients with preexisting heart disease is unknown. Hypotension may occur during administration, or up to two 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.

Those patients with a recent history of myocardial infarction and/or previous or current arrhythmic disorder, who require INTRON A therapy, should be closely monitored (see **Laboratory Tests**).

Central nervous system effects manifested by depression, confusion and other alterations of mental status were observed in about 2% of hairy cell leukemia patients treated with INTRON A. The overall incidence in a larger patient population with other malignancies treated with higher doses of INTRON A was 10%. More significant obtundation and coma have been observed in some patients, usually elderly, treated at higher doses for other malignant diseases. These effects are usually rapidly reversible. In a few severe episodes, full resolution of symptoms has taken up to three weeks. Patients should be closely monitored until resolution of these effects. Discontinuation of INTRON A therapy may be required. Narcotics, hypnotics, or sedatives may be used concurrently with caution.

Laboratory abnormalities which occurred in hairy cell leukemia patients included elevated SGOT and SGPT, which occurred in 4% and 13% of patients, respectively. The overall incidences of laboratory abnormalities in a larger patient population with other malignancies, and treated at higher doses were somewhat higher. These included elevated liver function tests (SGOT, SGPT in 10% of patients) and reductions in granulocyte (20% of patients) and platelet counts (18% of patients) (see **Laboratory Tests**). These abnormalities are usually mild to moderate and transient. Severe abnormalities of these laboratory parameters are usually rapidly reversible upon cessation or reduction of INTRON A therapy.

Condylomata Acuminata The 3 million, 5 million, and 25 million IU strengths are not to be used for the intralesional treatment of condylomata since the dilution required for the intralesional use would result in a hypertonic solution. The 50 million IU strength is not to be used for the treatment of condylomata.

AIDS-Related Kaposi's Sarcoma INTRON A 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 (AZT). 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 Non-A, Non-B/C (NANB/C) INTRON A therapy is not recommended for the treatment of patients with decompensated liver disease or immune suppressed transplant recipients, since safety and efficacy studies have not been conducted in these patient populations.

Patients with autoimmune hepatitis or a history of autoimmune disease should not be treated with INTRON A Interferon alfa-2b, recombinant for Injection.

Patients with a preexisting psychiatric condition or a history of severe psychiatric disorder should not be treated with INTRON A.[3] Therapy should be discontinued for any patient developing severe depression during treatment.

Patients with preexisting thyroid abnormalities whose thyroid function cannot be maintained in the normal range by medication should not be treated with INTRON A. Therapy should be discontinued for patients developing thyroid abnormalities during treatment whose thyroid function cannot be normalized by medication.

PRECAUTIONS

General Acute serious hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have not been observed, but might occur, in patients receiving INTRON A; however, 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.

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.

Drug Interactions Interactions between INTRON A and other drugs have not been fully evaluated. Caution should be exercised when administering INTRON A in combination with other potentially myelosuppressive agents.

Information for Patients Patients being treated with INTRON A Injection 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 treatment for AIDS-Related KS 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** section) and appear to decrease in severity as treatment continues. Some of these "flu-like" symptoms may be minimized by bedtime administration. Acetaminophen may be used to prevent or partially alleviate the fever and headache.

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

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 complete blood counts and differential as well as platelet counts.
- Blood chemistries—electrolytes and liver function tests.

Those patients who have preexisting cardiac abnormalities and/or are in advanced stages of cancer, should have electro-

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