

PRODUCT MONOGRAPH

 **INTRON A[®]**

interferon alfa-2b

Lyophilized Powder with Diluent:

10 million IU interferon alfa-2b/vial

18 million IU interferon alfa-2b/vial

Ready-to-Use Solution (Albumin (human) free):

10 million IU interferon alfa-2b/vial (10 million IU/mL)

18 million IU interferon alfa-2b/vial (6 million IU/mL)

25 million IU interferon alfa-2b/vial (10 million IU/mL)

Solution for Injection (Albumin (human) free), Multi-Dose Pen:

18 million IU interferon alfa-2b/pen (15 million IU/mL)

30 million IU interferon alfa-2b/pen (25 million IU/mL)

60 million IU interferon alfa-2b/pen (50 million IU/mL)

Biological Response Modifier

Merck Canada Inc.
16750 route Transcanadienne
Kirkland, Quebec H9H 4M7

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interferon alfa-2b

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous; Intramuscular; Intralesional and Intravenous	Lyophilized Powder with diluent 10 million IU interferon alfa-2b/vial 18 million IU interferon alfa-2b/vial	For a complete listing see <i>Dosage Forms, Composition and Packaging</i> section.
Subcutaneous; Intramuscular; and Intravenous	Ready-to-Use Solution (Albumin (human) free) 10 million IU interferon alfa-2b/vial (10 million IU/mL) 18 million IU interferon alfa-2b/vial (6 million IU/mL) 25 million IU interferon alfa-2b/vial (10 million IU/mL)	For a complete listing see <i>Dosage Forms, Composition and Packaging</i> section.
Subcutaneous	Solution for Injection (Albumin (human) free), Multi-Dose Pen 18 million IU interferon alfa-2b/pen (15 million IU/mL) 30 million IU interferon alfa-2b/pen (25 million IU/mL) 60 million IU interferon alfa-2b/pen (50 million IU/mL)	For a complete listing see <i>Dosage Forms, Composition and Packaging</i> section.

DESCRIPTION

INTRON A[®] (interferon alfa-2b) is a water-soluble protein produced by recombinant DNA techniques. It is obtained from a clone of *E. coli*, which has a genetically engineered plasmid hybridized with an interferon alfa-2b gene from human leukocytes.

INDICATIONS AND CLINICAL USE

- **Chronic Hepatitis C**

INTRON A[®] is indicated for the treatment of chronic hepatitis C in patients 18 years or older with compensated liver disease who have a history of blood or blood product exposure and/or are Hepatitis C Virus (HCV) antibody positive. Studies in these patients demonstrated that INTRON A[®] can produce normalization of serum alanine aminotransferase (ALT), clearance of serum HCV RNA and improvement in liver histology.

- **Chronic Active Hepatitis B**

INTRON A[®] is indicated for the treatment of chronic active hepatitis B in patients 18 years of age or older with compensated liver disease and who have evidence of viral replication. Patients must be serum hepatitis B surface antigen (HBsAg) positive for at least 6 months and have Hepatitis B Virus (HBV) replication, as demonstrated by positive serum HBeAg, with elevated serum ALT.

Studies in these patients demonstrated that INTRON A[®] therapy can produce virologic remission of this disease (loss of serum HBeAg and HBV-DNA), and normalization of serum aminotransferases. INTRON A[®] therapy resulted in the loss of serum HBsAg in some responding patients.

INTRON A[®] is not indicated for the treatment of patients who are chronic carriers of HBsAg but lack evidence of viral replication (serum HBeAg negative).

- **Chronic Myelogenous Leukemia**

INTRON A[®] is indicated for the treatment of patients with chronic myelogenous leukemia (CML). Studies have demonstrated a greater likelihood of response to INTRON A[®] therapy in patients who are in the chronic phase of the disease.

Thrombocytosis associated with CML: Thrombocytosis is frequently associated with CML. During the clinical experience accumulated to date, approximately one-quarter (26%) of the patients diagnosed with CML had concomitant thrombocytosis, with a baseline platelet count of greater than $500 \times 10^9/L$. Platelet control was achieved in all patients within two months of treatment. At no time were monthly platelet counts $< 80 \times 10^9/L$.

- **Multiple Myeloma**

INTRON A[®] maintenance is a therapeutic option for multiple myeloma patients who achieved objective remission on induction therapy (i.e., melphalan and prednisone). In the relatively older patient population, the potential interferon-mediated benefit of prolonged remission duration must be weighed against the toxicity associated with interferon therapy. The approach to these patients should be individualised.

- **Non-Hodgkin's Lymphoma**
INTRON A[®] is indicated as adjuvant treatment of high tumor burden follicular lymphoma (Stage 3 or 4) in combination with appropriate chemotherapy, such as a CHOP-like regimen.
- **Malignant Melanoma**
INTRON A[®] is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery.
- **AIDS-Related Kaposi's Sarcoma**
INTRON A[®] is 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.
- **Hairy Cell Leukemia**
INTRON A[®] is indicated for the treatment of patients with hairy cell leukemia either following or replacing splenectomy.
- **Basal Cell Carcinoma**
INTRON A[®], administered intralesionally, should be considered as an alternative treatment for patients with primary superficial and noduloulcerative basal cell carcinoma, where surgery or radiation are considered inappropriate. The basal cell lesion should be subtyped prior to initiation of treatment since no data exist for the use of INTRON A[®] in the following conditions: 1) recurrent basal cell carcinoma; 2) genetic or nevoid basal cell carcinoma; 3) basal cell carcinoma with evidence of deep tissue involvement; 4) morphealike basal cell carcinoma.
- **Condylomata Acuminata**
INTRON A[®] is indicated for intralesional treatment of selected patients with condylomata acuminata involving external surfaces of the genital and perianal areas.

In selecting patients for INTRON A[®] treatment, 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[®] therapy offers an additional approach to treatment in condylomata 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.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug, to any ingredient in the formulation or component of the container or to any interferon. For a complete listing, see the *Dosage Forms, Composition and Packaging* section of the product monograph.
- Patients with severe renal dysfunction (creatinine clearance < 50 mL/min) must not be treated with INTRON A[®] injection when used in combination with ribavirin.
- Patients with autoimmune hepatitis.
- Patients with a decompensated liver disease.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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 cases, but not all cases, these disorders resolve after stopping interferon therapy.

General

When INTRON A[®] Products are administered in combination with ribavirin in patients with chronic hepatitis C, please also refer to ribavirin product information. When INTRON A[®] is administered in combination with ribavirin, subjects with impaired renal function and/or those over the age of 50 should be more carefully monitored with respect to the development of anemia.

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.

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 (CVS) disease (e.g., unstable angina, uncontrolled congestive heart failure), pulmonary disease (e.g., chronic obstructive pulmonary disease), or diabetes mellitus prone to ketoacidosis.

Cardiovascular

Cardiovascular: Chest pain, hypertension, cardiac arrhythmia, cardiac ischemia, and myocardial infarction have been reported in patients with and without a history of cardiac disorder or abnormality in association with the use of alpha interferon therapies including INTRON A[®]. INTRON A[®] should not be administered to patients with a history of severe pre-existing cardiac

disease including unstable or uncontrolled cardiac disease in the previous 6 months. Patients with a history of cardiac disease (e.g., congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders) or with AIDS-Related Kaposi's Sarcoma, who require INTRON A[®] therapy, should be closely monitored (see *Monitoring and Laboratory Tests* section). Those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer, should have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) occurred rarely and appeared to be correlated with pre-existing conditions and prior therapy with cardiotoxic agents. These adverse experiences usually respond to conventional therapy but may require dose modification or discontinuation of INTRON A[®] therapy.

Transient reversible cardiomyopathy was reported in approximately 2% of the AIDS-Related Kaposi's Sarcoma patients treated with INTRON A[®]. Cardiomyopathy has also been reported in Acquired Immune Deficiency Syndrome (AIDS) patients not receiving INTRON A[®] therapy. Baseline chest X-rays are suggested and should be repeated if clinically indicated.

Hydration: Adequate hydration must be maintained in patients undergoing INTRON A[®] therapy since hypotension related to fluid depletion has been seen in some patients during therapy and up to two days post-therapy. Fluid replacement may be necessary.

Cerebrovascular Disorders

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

Dental and Periodontal Disorders

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

Endocrine and Metabolism

Hypertriglyceridemia: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed with INTRON A[®]. Monitoring of lipid levels is, therefore, recommended.

Thyroid Changes: Infrequently, patients treated with alpha interferons, including INTRON A[®] have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. After discontinuation of therapy, thyroid dysfunction may or may not be reversed. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, INTRON

A[®] treatment may be initiated or continued only if TSH levels can be maintained in the normal range by medication.

Diabetes Mellitus and Hyperglycemia: As with other alpha interferons, diabetes mellitus and hyperglycemia have been observed in patients treated with INTRON A[®]. Symptomatic patients should have their blood glucose measured and followed-up accordingly. Patients with diabetes mellitus may require adjustment of their anti-diabetic regimen (see *ADVERSE REACTIONS* section).

Gastrointestinal

Colitis: As seen with other interferons, colitis, sometimes serious, have been observed within 12 weeks of starting INTRON A[®] therapy. INTRON A[®] should be discontinued immediately if symptoms of colitis develop (typical manifestations include abdominal pain, bloody diarrhea and fever). The colitis usually resolves within 1 to 3 weeks of discontinuation of alpha interferon.

Hepatic/Biliary/Pancreatic

Liver Function-Chronic Hepatitis C and Chronic Active Hepatitis B: Patients with decompensated liver disease (including prolongation of coagulation markers or other markers of hepatic function), autoimmune hepatitis, a history of autoimmune disease or immune suppressed transplant recipients should not be treated with INTRON A[®]. There are reports of worsening liver disease, including jaundice, hepatic encephalopathy, hepatic failure and death following INTRON A[®] therapy in patients with decompensated liver disease. INTRON A[®] increases the risk of hepatic decompensation and death in patients with cirrhosis.

Patients with chronic hepatitis B with evidence of decreasing hepatic synthetic function, such as decreasing albumin levels or prolongation of prothrombin time, who nevertheless meet the criteria for therapy, may be at increased risk of clinical decompensation if a flare of aminotransferases occurs. In considering these patients for INTRON A[®] therapy, the potential risks must be evaluated against the potential benefits of treatment.

Monitor hepatic function with serum bilirubin, ALT (alanine transaminase), AST (aspartate aminotransferase), alkaline phosphatase and LDH (lactate dehydrogenase) at 2, 8, and 12 weeks following initiation of INTRON A[®], then every 6 months while receiving INTRON A[®]. Permanently discontinue INTRON A[®] for evidence of severe (Grade 3) hepatic injury or hepatic decompensation (Child-Pugh score >6 [class B and C]).

Hepatic Function: Hepatotoxicity resulting in fatality has been observed rarely in INTRON A[®] treated patients. Any patient developing liver function abnormalities or hepatopathy during treatment should be monitored closely and if appropriate, treatment should be discontinued.

Pancreatitis: Pancreatitis, sometimes life-threatening, has occurred in patients treated with alpha interferons including INTRON A[®]. INTRON A[®] therapy should be suspended if symptoms or signs of pancreatitis are observed. INTRON A[®] should be discontinued in patients diagnosed with pancreatitis.

Immune

AIDS-Related Kaposi's Sarcoma: INTRON A[®] should not be used for patients with rapidly progressive visceral disease. Patients receiving concomitant zidovudine (AZT) have had a higher incidence of neutropenia than that expected with AZT alone. Careful monitoring of the WBC counts is indicated in all patients who are myelosuppressed and in all patients receiving other myelosuppressive medications. The effects of INTRON A[®] when administered in association with drugs used in the treatment of AIDS-Related disease are unknown.

Autoimmune disease: The development of different auto-antibodies has been reported during treatment with alpha interferons including INTRON A[®]. Clinical manifestations of autoimmune disease during interferon therapy including INTRON A[®], may occur more frequently in patients predisposed to the development of autoimmune disorders.

Transplantation: The safety and efficacy of INTRON A[®] treatment have not been established for patients with liver or other organ transplants. Preliminary data indicates that interferon alpha, including INTRON A[®] therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported but a causal association with interferon alpha or INTRON A[®] has not been established.

Fever: While fever may be associated with interferon therapy, other causes of persistent fever should be ruled out. Caution should also be observed in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Neurologic

Effects on Ability to Drive and Use Machines: Patients who develop fatigue, somnolence or confusion during treatment with INTRON A[®] therapy are cautioned to avoid driving or operating machinery.

Ophthalmologic

Ocular changes: **As with other alpha interferons, ophthalmologic disorders, including retinopathies (including macular edema), retinal hemorrhages, cotton wool spots, retinal artery or vein obstruction, serous retinal detachment, loss of visual acuity or visual field, optic neuritis and papilledema have been reported in rare instances after treatment with INTRON A[®] (see ADVERSE REACTIONS section).** All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Because these ocular events may occur in conjunction with other disease states, periodic visual examinations during INTRON A[®] therapy are recommended in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of INTRON A[®] should be considered in patients who develop new or worsening ophthalmological disorders.

Psychiatric

Psychiatric and Central Nervous System (CNS):

Patients with existence of or history of severe psychiatric conditions: Patients with a pre-existing psychiatric condition or a history of severe psychiatric disorder should not be treated with INTRON A[®]. If treatment with INTRON A is judged necessary in adult patients with existence or

history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualized diagnostic and therapeutic management of the psychiatric condition. Patients should be monitored and therapy discontinued for any patient developing severe depression and suicidal behaviour, and psychosis including hallucinations and aggressive behaviour during treatment.

If severe neuropsychiatric effects, particularly depression, are observed, INTRON A[®] therapy should be discontinued. CNS effects manifested by depression, confusion and other alterations of mental status have been observed in some INTRON A[®]-treated patients; suicidal ideation, attempted suicide and aggressive behavior sometimes directed towards others have been observed rarely. These adverse effects have occurred in patients treated with recommended doses as well as in patients treated with higher INTRON A[®] doses. More significant obtundation and coma have been observed in some patients, usually elderly, treated at higher doses. While these effects are generally reversible upon discontinuation of therapy, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of INTRON A[®]. If patients develop psychiatric problems or CNS problems, including clinical depression, it is recommended that the patients be carefully monitored by the prescribing physician during treatment and in the 6 month-follow-up period, due to the potential seriousness of these undesirable effects. Consideration should be given to discontinue therapy, if psychiatric intervention and/or dose reduction is unsuccessful in controlling psychiatric symptoms. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation or aggressive behavior towards others is identified, it is recommended that treatment with INTRON A[®] be discontinued and the patient followed, with psychiatric intervention as appropriate.

Patients with substance use/abuse: HCV infected patients having a co-occurring substance use disorder (alcohol, cannabis, etc.) are at an increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders when treated with alpha interferon. If treatment with alpha interferon is judged necessary in these patients, the presence of psychiatric co-morbidities and the potential for other substance use should be carefully assessed and adequately managed before initiating therapy. If necessary, an inter-disciplinary approach including a mental health care provider or addiction specialist should be considered to evaluate, treat and follow the patient. Patients should be closely monitored during therapy and even after treatment discontinuation. Early intervention for re-emergence or development of psychiatric disorders and substance use is recommended.

Renal

Renal Function: Patients with severe renal dysfunction (creatinine clearance < 50 mL/min) should be monitored closely during treatment with INTRON A[®]. Increases in serum creatinine levels have been observed in patients with renal insufficiency treated with interferons, including INTRON A[®]. Patients with impairment of renal function should be closely monitored for signs and symptoms of toxicity, including increases in serum creatinine, and careful adjustments of doses are required.

Respiratory

Pulmonary Changes: As with other alpha interferons, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia, occasionally resulting in fatality, have been observed rarely in INTRON A[®] treated patients. The etiology has not been defined. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient should be monitored closely, and, if appropriate, interferon-alpha treatment should be discontinued. While this has been reported more often in patients with chronic hepatitis C treated with interferon-alpha, it has also been reported in patients with oncologic diseases treated with interferon-alpha. Prompt discontinuation of interferon alpha administration and supportive treatment (including treatment with corticosteroids) appear to be associated with resolution of pulmonary events. Moreover, these symptoms have been reported more frequently when *Shosaikoto (Xiao-Chai-Hu-Tang)*, a Chinese herbal medication, has been administered concomitantly with interferon-alpha.

Sensitivity/Resistance

Acute Hypersensitivity: Acute serious hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to INTRON A[®] have been observed rarely during INTRON A[®] therapy. If such a reaction develops, the drug should be discontinued and appropriate medical therapy instituted immediately. Transient rashes do not necessitate interruption of treatment.

INTRON A Ready-to-Use Solution (Albumin (human) free) and Solution for Injection (Albumin (human) free) Multi-Dose Pen contain m-cresol as preservative; some patients may experience allergic reaction to this ingredient.

Sexual Function/Reproduction

INTRON A[®] has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the intramuscular (IM) or subcutaneous (SC) dose of 2 million IU/m². Although abortion was observed in all dose groups (7.5 million, 15 million, and 30 million IU/kg), it was only statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the IM or SC dose of 2 million IU/m²). High doses of other forms of interferons alpha and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys. There are no adequate and well controlled studies on the use of INTRON A[®] in pregnant women. INTRON A[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Effect on Fertility: Interferons, including INTRON A[®] may impair fertility. In studies of interferon use in non-human primates, menstrual cycle abnormalities have been observed. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon. Therefore, fertile women should not receive INTRON A[®] unless they are using effective contraception during the treatment period. The effects of INTRON A[®] on male fertility have not been studied. Therefore, a possible effect on male fertility should be considered.

Skin

Psoriatic Disease and Sarcoidosis: Use of alpha interferons including INTRON A[®], has been associated with exacerbating pre-existing psoriatic disease and sarcoidosis. Use of INTRON A[®] in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Immunological Effects: A number of immune-mediated dermatological reactions associated with the use of alpha interferons have been reported ranging from erythema multiforme to more severe but very rare occurrences of Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Special Populations

Pregnant Women: There are no adequate and well controlled studies on the use of INTRON A[®] in pregnant women. INTRON A[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Combination therapy with ribavirin: Ribavirin causes serious birth defects or fetal death when administered during pregnancy. Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking INTRON A[®] in combination with ribavirin.

Nursing Women: It is not known whether INTRON A[®] is excreted in human milk. However, studies in mice have shown that mouse interferons are excreted into the milk, and because of the potential for serious adverse reactions from INTRON A[®] in nursing infants, a decision to use or discontinue the drug should be based on a benefit to risk assessment.

Pediatrics: Safety and effectiveness of INTRON A[®] have not been established in patients below the age of 18 years.

Monitoring and Laboratory Tests

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 (WBC) counts and platelet count.
- Blood chemistries: including electrolytes, calcium, liver enzyme tests, serum creatinine and thyroid function.

The hematologic parameters of the patients should be followed closely as part of the treatment because a certain degree of myelodepression, including very rare incidences of aplastic anemia and pancytopenia, has been detected in some patients under treatment with INTRON A[®].

Mild to moderate leukopenia and elevated serum liver enzyme (AST) levels have been reported with intralesional administration of INTRON A[®]; therefore, the monitoring of these laboratory parameters should be considered.

For specific laboratory testing recommendations on chronic hepatitis C and chronic active hepatitis B, see the *DOSAGE AND ADMINISTRATION* section.

ADVERSE REACTIONS

Overview

The most common adverse reactions were “flu-like” symptoms.

Adverse Drug Reactions

Systemic administration:

The most commonly reported adverse effects were fever, fatigue, headache and myalgia (“flu-like” symptoms). Fever and fatigue were reversible within 72 hours of interruption or cessation of treatment and were dose related. While fever may be related to the “flu-like” symptoms commonly reported in patients treated with interferons, other causes of persistent fever should be excluded.

Common adverse effects include rigors/chills, anorexia and nausea. Less common adverse effects include vomiting, diarrhea, arthralgia, asthenia, somnolence, dizziness, dry mouth, alopecia, “flu-like” symptoms (unspecified), back pain, musculoskeletal pain, depression, suicidal ideation, suicide attempts, suicide, malaise, pain, increased sweating, taste alteration, irritability, insomnia, confusion, impaired concentration and hypotension.

Rarely reported adverse reactions include abdominal pain, right upper quadrant (RUQ) pain, rash (e.g., erythematous and maculopapular), nervousness, injection site disorders, paresthesia, viral infection, herpes simplex, dry skin, erythema, pruritus, conjunctivitis, eye pain, abnormal/blurred vision, lacrimal gland disorder, anxiety, emotional lability, psychosis including hallucinations, aggressive behavior sometimes directed towards others, agitation, epistaxis, migraine, nasal congestion, sinusitis, rhinitis, coughing, pharyngitis, resistance mechanism disorders (e.g., altered resistance to infection; these effects rarely have been life-threatening or fatal), respiratory disorders, pulmonary infiltrates, pneumonitis and pneumonia, seizures, impaired consciousness, weight decrease, facial edema, dyspnea, dyspepsia, chest pain, tachycardia, hypertension, increased appetite, decreased libido, menstrual disorders (e.g., amenorrhea, menorrhagia), hypoesthesia, taste perversion, glossitis, stomatitis, loose stool, constipation, gingival bleeding, leg cramps, peripheral ischemia, neuropathy, polyneuropathy, peripheral neuropathy, rhabdomyolysis (sometimes serious), hearing disorder, vertigo, hyperuricemia, and renal insufficiency. Hyperthyroidism or hypothyroidism have also been observed rarely. Hepatotoxicity, including fatality, has been observed rarely. (See *WARNINGS AND PRECAUTIONS* section.)

Retinal hemorrhages, retinopathies (including macular edema), cotton-wool spots, and retinal artery or vein obstruction; loss of visual acuity or visual field, optic neuritis, and papilledema have been observed rarely in patients treated with interferon alpha, including INTRON A[®] (see *WARNINGS AND PRECAUTIONS* section).

Very rarely following the marketing of INTRON A[®], cases of nephrotic syndrome, renal failure, aggravated diabetes mellitus, diabetes mellitus, hyperglycemia, colitis, pancreatitis, hypertriglyceridemia, hearing disorders, cardiac ischemia, myocardial infarction, pericarditis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis and injection site necrosis have been reported.

CVS adverse reactions, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior cardiotoxic therapy. Transient reversible cardiomyopathy has been reported rarely in patients without prior evidence of cardiac disease. Very rarely reported adverse reactions include pancreatitis, cardiac ischemia and myocardial infarction.

When INTRON A[®] is used with hydroxyurea, the occurrence of cutaneous vasculitides may be increased.

Very rarely INTRON A[®] used alone or in combination with ribavirin may be associated with aplastic anemia or pure red cell aplasia.

Very rarely sarcoidosis or exacerbation of sarcoidosis has been reported. Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU (MIU) daily, include reduction in granulocyte and WBC counts; decreases in hemoglobin level and platelet count; increases in alkaline phosphatase, lactate dehydrogenase (LDH), serum creatinine, serum urea nitrogen, and TSH levels. Moderate and usually reversible reduction in all three blood elements - white blood cells, red blood cells and platelets, have been reported. Increase in serum ALT/AST (SGPT/SGOT) levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with chronic hepatitis B coincident with clearance of viral DNAp.

There were no new or unusual toxicities associated with the use of INTRON A[®] for the treatment of malignant melanoma. The most commonly reported adverse reactions were gastrointestinal events, hematologic events, hepatic toxicity, neurologic toxicity, vomiting, chills, fatigue, fever and myalgia. In the surgical adjuvant trial involving 280 patients, 100% of patients treated with INTRON A[®] experienced at least one adverse event compared to 43% for the observation patients. Severe adverse events occurred in 78% of INTRON A[®] treated patients versus 6% of observation patients. 65% of patients had at least one dose modification due to toxicity. 24% of patients discontinued INTRON A[®] treatment due to adverse events.

The following adverse reactions were reported to be possibly or probably treatment-related in the trial involving 143 INTRON A[®] treated patients. The most commonly reported adverse reactions were fatigue, fever, myalgia, anorexia, nausea, headache and chills. Less common adverse reactions were depression, diarrhea, alopecia, taste alteration, dizziness, rash, pain (unspecified), dyspnea, paresthesia, influenza-like symptoms, confusion, bleeding, coughing, increased sweating, arthralgia, malaise and insomnia.

Intralesional administration:

Most reported adverse reactions were mild to moderate, transient and rapidly reversible. The incidence of reported adverse reactions in the patients treated for condylomata acuminata appears to increase in proportion to the number of lesions treated and consequently, is dose related.

The most common adverse reactions were “flu-like” symptoms, (rigors/chills fever, headache, myalgia and malaise). Other commonly reported side effects included nausea, fatigue, dizziness, arthralgia, back pain and injection site reactions (burning, itching, pain and injection site bleeding). In patients treated for condylomata acuminata injection site reactions appeared to be due to manipulation of the lesion rather than the INTRON A[®] therapy.

Rarely reported side effects include diarrhea, somnolence, depression, pain, dyspepsia, increased sweating, unspecified “flu-like” symptoms, confusion, weakness, vomiting, flushing, leg cramps, asthenia, taste perversion, dermatitis and pruritus.

Low WBC counts, elevated serum liver enzyme (AST/SGOT) levels and low platelet counts have been reported in some patients with intralesional administration of INTRON A[®]. Most of these laboratory findings were transient, rapidly reversible and mild to moderate in severity.

Reported adverse reactions and abnormal laboratory test values observed in patients who were re-treated for condylomata acuminata with INTRON A[®] were qualitatively and quantitatively similar to those reported above.

The following adverse events have been reported very rarely after administration of INTRON A[®]:

Blood Disorders: hemolytic anemia, granulocytopenia, leukopenia, increased gamma globulins, coagulation disorder.

Body as a Whole: dehydration, hypercalcemia, cachexia, peripheral edema, lymphadenopathy, periorbital edema, malignant hyperpyrexia, transplant rejection, acidosis, ascites.

CVS: palpitations, postural hypotension, chest pain, chest pain substernal, bradycardia, cardiac failure, cardiomyopathy, atrial fibrillation, arrhythmia, extrasystole, angina pectoris, thrombophlebitis, peripheral ischemia.

Central and Peripheral Nervous System: amnesia, stupor, convulsions, hypertonia, hyperesthesia, hot flashes, migraine, encephalopathy, tremor, coma, extrapyramidal disorder, paresis, speech disorder, dysphonia, syncope, tinnitus, vertigo, abnormal coordination, ataxia, aphasia, CNS dysfunction, abnormal gait, hyperkinesia, dystonia, paralysis, hyperparesthesia.

Endocrine System: gynecomastia, virilism, aggravation of diabetes mellitus, hyperglycemia, adrenal hypercorticism.

Gastrointestinal System: eructation, stomatitis, stomatitis ulcerative, constipation, tenesmus, ileus, thirst, melena, increased saliva, esophagitis, rectal bleeding after stool, dysphagia,

gastrointestinal hemorrhage, gastric ulcer, gingivitis, gum hyperplasia, rectal hemorrhage, oral leukoplakia, gastrointestinal mucosal discoloration, abdominal distention, flatulence, tongue discoloration, glossitis, taste loss, discolored feces.

Liver and Biliary System: abnormal hepatic function tests, bilirubinemia, jaundice, RUQ pain, hepatosplenomegaly, splenomegaly, hepatic encephalopathy.

Musculoskeletal System: bone pain, muscle weakness, arthritis, arthrosis, myopathy.

Psychiatric Disorders: agitation, emotional lability, personality disorder, abnormal thinking, abnormal dreaming, sleep disorder, dysphonia, flushing, hypokinesia, suicide attempt, paroniria, apathy, aggravated depression, neurosis, aggressive reaction, feeling of ebriety, psychosis including hallucination, dementia, paranoid reactions.

Reproduction System: impotence, leukorrhea, menorrhagia, uterine bleeding, vaginal hemorrhage, amenorrhea.

Resistance Mechanism Disorders (i.e., altered resistance to infection): stye, conjunctivitis, viral and fungal infections, moniliasis, sepsis.

Respiratory System: hypoxia, stridor, nasal congestion, pneumonia, sinusitis, rhinitis, rhinorrhea, bronchospasm, cyanosis, wheezing, pleural pain, sneezing, nonproductive coughing, pulmonary embolism, pulmonary edema, laryngitis, cold.

Skin and Appendages: urticaria, acne, nail disorders, hypertrichosis, purpura, peripheral ischemia, furunculosis, non-herpetic cold sores, epidermal necrolysis, lacrimal gland disorder, cyanosis of the hand, photosensitivity, skin discoloration, chloasma, abnormal hair texture, increased hair growth, skin depigmentation, dermatitis lichenoides, melanosis, vitiligo, dry skin, dermatitis, erythema, maculopapular rash, pustular rash, clammy skin, injection site reaction.

Urinary System: micturition disorder, nocturia, polyuria, hematuria, micturition frequency, cystitis, oliguria, nephrosis, urinary incontinence, hyperuricemia.

Visual and Auditory Disorders: photophobia, blurred vision, abnormal vision, diplopia, dry eyes, oculomotor nerve paralysis, retinal disorder, retinal hemorrhage, night blindness, twitching, earache, deafness, hyperacusis.

Post-Market Adverse Drug Reactions

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and Vogt-Koyanagi-Harada syndrome.

Cases of acute hypersensitivity reactions, including anaphylaxis, urticaria, and angioedema have been reported.

Asthenic conditions (including asthenia, malaise and fatigue), homicidal ideation, dehydration, palpitations, psoriasis, fungal infection, bacterial infection (including sepsis), serous retinal detachment, pulmonary fibrosis and hepatitis B reactivation in HCV/HBV co-infected patients have been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

Administration of INTRON A[®] in combination with other chemotherapeutic agents may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered drug. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhea, neutropenia, renal impairment, and electrolyte disturbance. Because of the risk of increased toxicity, careful adjustments of doses are required for INTRON A[®] and for the concomitant chemotherapeutic agents.

An increased risk of developing peripheral neuropathy cannot be ruled out for treatments combining telbivudine with any alfa (standard or pegylated types) and beta interferon products. This risk might occur when the drug is used with interferon products other than pegylated interferon alfa-2a. Development of peripheral neuropathy was reported in a small clinical trial in Hepatitis B investigating the use of both 600 mg daily of telbivudine and 180 micrograms once weekly by subcutaneous administration of pegylated interferon alfa-2a. The safety and efficacy of telbivudine in combination with interferon alfa-2b has not been established in patients with Hepatitis B; therefore, telbivudine in combination with alpha interferons is not recommended.

Concomitant Therapy

Acetaminophen (paracetamol) has been used successfully to alleviate the symptoms of fever and headache, which can occur with INTRON A[®] therapy. The recommended acetaminophen dosage is 500 mg to 1 g given 30 minutes before administration of INTRON A[®]. The maximum dosage of acetaminophen to be given is 1 g four times daily. In order to properly assess the source of fever, adjunctive acetaminophen should be limited to a maximum of 5 consecutive days unless otherwise specified by the prescribing physician.

Narcotics, hypnotics or sedatives should be administered with caution concomitantly with INTRON A[®] Injection.

A synergistic adverse effect on the WBC count may occur when INTRON A[®] is administered concomitantly with AZT. Patients receiving the two agents concomitantly have had a dose-dependent higher incidence of neutropenia than expected when AZT is administered alone.

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.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

As with other alpha interferons, pulmonary infiltrates, pneumonitis and pneumonia, occasionally resulting in fatality, have been observed rarely in INTRON A[®] treated patients. These symptoms have been reported more frequently when *Shosaikoto (Xiao-Chai-Hu-Tang)*, a Chinese herbal medication, has been administered concomitantly with interferon-alpha.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

INTRON A[®] may be administered using either sterilized glass or plastic disposable syringes or the INTRON A[®] Multi-Dose Pen.

In general, the dosage may be adjusted according to the patient's tolerance to the medication. If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or if the disease progresses rapidly, treatment with INTRON A[®] should be discontinued.

For maintenance dosage regimens administered subcutaneously or intramuscularly, the patient may self-administer the dose at the discretion of the physician.

Laboratory Tests: Standard hematologic tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, including serum ALT, serum bilirubin, and albumin, serum protein, and serum creatinine) should be conducted in all patients prior to and periodically during treatment with INTRON A[®]. TSH levels must be within normal limits prior to initiation of INTRON A[®] therapy. Any patient developing symptoms consistent with possible thyroid dysfunction during INTRON A[®] therapy should have an evaluation of thyroid function.

In patients treated for hepatitis, the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares (≥ 2 times baseline) during INTRON A[®] therapy, INTRON A[®] may be continued unless signs or symptoms of liver failure are observed. During ALT flare, liver function tests for prothrombin time, ALT, alkaline phosphatase, albumin and bilirubin levels should be performed at two-week intervals.

Recommended Dose and Dosage Adjustment

Chronic Hepatitis C: The recommended dosage of INTRON A[®] is 3 MIU administered subcutaneously or intramuscularly three times per week (every other day) for up to 18 months. Most patients who respond demonstrate improvement in serum ALT levels within 12 weeks. Some patients who fail to respond to 3 MIU may benefit from higher doses of up to 10 MIU three times per week (every other day).

Current clinical experience in patients who remain on INTRON A[®] for 12 - 18 months indicates that a higher proportion of patients demonstrated a sustained response after longer durations of therapy than those who discontinued therapy after six months.

Patients who relapse following INTRON A[®] therapy may be retreated with the same dosage regimen to which they had previously responded.

Patients should be tested for the presence of antibody to HCV and 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 bilirubin, serum albumin, and serum creatinine should be within normal limits.

Prior to initiation of INTRON A[®] therapy, CBC and platelet counts should be evaluated in order to establish baselines for monitoring potential toxicity. During treatment with INTRON A[®], these tests should be repeated at weeks 1 and 2, and monthly thereafter.

ALT levels should be evaluated after 2, 4, 12 and 24 weeks of therapy to assess response to treatment.

TSH must be within normal limits upon initiation of INTRON A[®] treatment. Patients with pre-existing thyroid abnormalities may be treated if TSH levels can be maintained in the normal range by medication.

Adults- HCV/HBV co-infection: The safety and efficacy of INTRON A[®] alone or in combination with boceprevir or ribavirin for the treatment of chronic hepatitis C genotype 1 infection in patients co-infected with hepatitis B Virus (HBV) and HCV have not been studied.

Chronic Active Hepatitis B: The recommended dosage of INTRON A[®] is 30 to 35 MIU per week, administered subcutaneously or intramuscularly either as 5 MIU daily or 10 MIU three times per week (every other day), for 16 weeks.

Prior to initiation of INTRON A[®] therapy, a liver biopsy may be useful in establishing a diagnosis of chronic hepatitis. 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:

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other clinical signs of decompensation
- Bilirubin Normal
- Albumin Stable and within normal limits
- Prothrombin time < 3 seconds prolonged
- WBC $\geq 4000/\text{mm}^3$
- Platelets $\geq 100,000/\text{mm}^3$

Patients with other causes of chronic hepatitis should be excluded. 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 and monthly thereafter. Liver function tests, including serum ALT, albumin and bilirubin, should be evaluated after 1, 2, 4, 8, 12, and 16 weeks of therapy. HBeAg, HBsAg, and ALT should be evaluated at the end of therapy, as well as at 3 and 6 months posttherapy, since patients may become virologic responders during the 6 month period following the end of treatment.

For patients with decreases in granulocyte or platelet counts, the following guidelines for dose modifications were used in the clinical trials:

<u>Dose</u>	<u>Granulocytes</u>	<u>Platelets</u>
Reduce 50%	< 750/mm ³	< 50,000/mm ³
Interrupt	< 500/mm ³	< 30,000/mm ³

INTRON A[®] therapy was resumed at 50% or increased to 100% of the initial dose when granulocytes and/or platelets increased above the appropriate values.

A transient increase in ALT ≥ 2 times baseline value (flare) can occur during INTRON A[®] therapy for chronic active hepatitis B. In clinical trials, this flare generally occurred 8 to 12 weeks after initiation of therapy and was more frequent in responders (63%, 24/38) than in nonresponders (27%, 13/48). However, coincident elevation in bilirubin ≥ 3 mg/dL occurred infrequently (2%, 2/85). When ALT flare occurs, in general INTRON A[®] therapy should be continued unless signs and symptoms of liver failure are observed. During ALT flare, clinical symptomatology and liver function tests including ALT, albumin and bilirubin, should be monitored at approximately 2 week intervals.

Chronic Myelogenous Leukemia: The recommended dosage of INTRON A[®] is 4 to 5 MIU/m² administered daily subcutaneously. Dosages as little as 0.5 MIU/m² or as high as 10 MIU/m² may be necessary to achieve or maintain control of the WBC count. When the WBC count is controlled, the dosage may be administered three times per week (every other day). The dosage may be adjusted according to the patient's tolerance to the medication.

Treatment should be initiated as early as possible after diagnosis, and continued until complete hematological response is achieved or for a maximum of 18 months. Responding patients generally show a hematologic response within two to three months of treatment. These patients should continue to be treated until a complete hematologic response is obtained, as defined by a WBC count of 3 to 4 x 10⁹/L. All patients with a complete hematological response should further continue treatment in order to achieve a cytogenetic response which in some patients may not occur until two years after treatment initiation.

In patients, who at the time of initiation of therapy with INTRON A[®], present with extremely high WBC counts leading to possible life-threatening complications, consideration should be given to concomitant interventions such as leukapheresis in order to quickly lower the WBC count. Once the immediate risk to the patient has been reduced, INTRON A[®] therapy should be initiated.

Thrombocytosis associated with CML: The recommended dosage for the control of thrombocytosis in CML is the same as that recommended above for the treatment of CML. Dose adjustments made for the control of the WBC counts should also be appropriate to control platelet counts.

Multiple Myeloma: In patients who are in the plateau phase following induction chemotherapy, INTRON A[®] may be administered as monotherapy, subcutaneously, at a dose of 3 MIU/m², three times a week (every other day).

Treatment should continue unless clear disease progression or severe intolerance occurs.

Non-Hodgkin's Lymphoma: When used adjunctively with chemotherapy, the recommended dosage of INTRON A[®] is 5 MIU three times a week on alternate days administered subcutaneously for a duration of 18 months.

The standard chemotherapeutic treatment for patients with high tumor burden follicular lymphomas is the administration of a combination chemotherapy regimen. Most of these regimens are related to the well-known CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone] regimen such as the CHVP regimen of doxorubicin, cyclophosphamide, teniposide and prednisolone.

At diagnosis, most follicular lymphoma patients have a disseminated disease, stage III or stage IV. Despite this advanced disease, many patients have an indolent course and survive several years after diagnosis. A wait and watch approach may be appropriate for these patients, especially if their tumor burden is low. Treatment is frequently initiated without delay for patients with high-tumor burden such as bulky lymphadenopathy, major organ obstruction or compression syndromes, malignant effusions, bone marrow failure, or rapidly enlarging tumors.

Malignant Melanoma: The recommended INTRON A[®] treatment regimen includes an induction treatment of 5 consecutive days per week for 4 weeks as an intravenous (IV) infusion at a dose of 20 MIU/m², followed by a maintenance treatment of 3 times per week for 48 weeks as a SC injection, at a dose of 10 MIU/m². Therapy should be administered for a total of one year unless the disease progresses.

Induction therapy is administered as a 20 minute IV infusion of INTRON A[®] in 100 mL of normal saline.

If severe adverse reactions develop during INTRON A[®] treatment, particularly if granulocytes decrease to <500/mL or ALT/AST rises to >5 x upper limit of normal, treatment should be temporarily discontinued until the adverse reaction abates. INTRON A[®] treatment should be restarted at 50% of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mL or ALT/AST rises to >10 x upper limit of normal, INTRON A[®] therapy should be discontinued. In the clinical trial, patients were able to maintain clinical benefit in conjunction with appropriate dose modifications.

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

AIDS-Related Kaposi's Sarcoma: The recommended dosage of INTRON A[®] is 30 MIU/m² three times a week (every other day) administered subcutaneously or intramuscularly. When patients initiate therapy at 30 MIU/m² three times per week, the average dose tolerated at the end of 12 weeks of therapy is approximately 75% of the weekly dose and 50% of the weekly dose at the end of 24 weeks of therapy.

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.

Hairy Cell Leukemia: The recommended dosage of INTRON A[®] is 2 MIU/m² administered subcutaneously three times a week (every other day).

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. The normalization of one or more hematologic variables usually begins within 2 months of initiation of therapy. Improvement in all three hematologic variables (granulocyte count, platelet count and hemoglobin level) may require 6 months or more of therapy.

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 the laboratory parameters have been stable for about 3 months. It is not known whether continued treatment after that point is beneficial.

Basal Cell Carcinoma: The lesion to be injected should be cleaned first with a sterile alcohol pad. The intralesional injection should be made into the base and substance of the lesion using a fine needle (30 gauge) and a 1 mL syringe. Care should be taken not to go too deeply beneath the lesion. SC injection should be avoided. For lesions with an initial area below 2 cm², inject 0.15 mL of reconstituted solution containing 1.5 MIU INTRON A[®] (see *Reconstitution* section) into the lesion three times a week on alternate days, for three weeks. The cumulative dose administered per lesion should be 13.5 MIU. As many as three lesions can be treated at one time.

Large superficial and noduloulcerative basal cell lesions (lesions with an area between two and ten cm²) should be treated three times a week (every other day) for three weeks with 0.5 MIU/cm² of the lesion's initial size (the minimum dose being 1.5 MIU and the maximum dose being 5.0 MIU). Only one large lesion should be treated at a time.

The improvement in clinical status (appearance, size, erythema, etc) of the treated lesion is a reliable predictor of biopsy-proven cures. Therefore, the clinical status should be monitored periodically after treatment end. Improvement in disease signs usually begins at approximately eight weeks after treatment initiation. If no clinical improvement on the lesion is observed after eight to twelve weeks, excision should be re-considered.

Condylomata Acuminata: Inject 1.0 MIU of INTRON A[®] (0.1 mL of reconstituted INTRON A[®] solution) into each lesion three times per week on alternate days, for 3 weeks. Only the 10 MIU vial of INTRON A[®] when reconstituted with 1 mL of designated diluent results in an isotonic solution at the desired concentration of 1 MIU per 0.1 mL. The injection should be administered intralesionally using a Tuberculin or similar syringe and a 25-30 gauge needle. The needle should be directed at the center of the base of the wart and at an angle almost parallel to the plane of the skin (approximating that in the commonly used PPD test). This will deliver the interferon to the dermal core of the lesion, infiltrating the lesion and causing a small wheal. Care should be taken not to go beneath the lesion too deeply; SC injection should be avoided, since this area is below the base of the lesion. Do not inject too superficially since this will result in possible leakage, infiltrating only the keratinized layer, and not the dermal core. As many as 5 lesions can be treated at one time. To reduce side effects, INTRON A[®] injections may be administered in the evening, when possible. Additionally, acetaminophen may be administered at the time of injection to alleviate some of the potential side effects.

The maximum response usually occurs 4 to 8 weeks after initiation of the first treatment course. If results at 12 to 16 weeks after the initial treatment course has concluded are not satisfactory, a second course of treatment using the above dosage schedule may be instituted providing that clinical symptoms and signs, or changes in laboratory parameters (liver function tests, WBC and platelets) do not preclude such a course of action.

Patients with six to ten condylomata may receive a second (sequential) course of treatment at the above dosage schedule, to treat up to five additional condylomata per course of treatment. Patients with greater than ten condylomata may receive additional sequences depending on how large a number of condylomata are present.

Administration

INTRON A[®] Lyophilized Powder

INTRON A lyophilized powder should be reconstituted with 1 mL of the accompanying sterile water for injection, as diluent.

The reconstituted solution is clear and colorless to light yellow in color. The reconstituted material, as for all parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

For SC or IM administration: Following reconstitution, the appropriate dose should be withdrawn with a sterile syringe and injected slowly subcutaneously or intramuscularly.

For intralesional administration: An isotonic solution of INTRON A[®] is recommended for the treatment of basal cell carcinoma. Only the 10 MIU vial of INTRON A[®] when reconstituted

with 1 mL of designated diluent results in an isotonic solution at the desired concentration of 1 MIU per 0.1 mL. Reconstitution of other vial sizes to prepare the dilution required for intralesional use will result in a hypertonic solution.

For IV administration: Following reconstitution, the calculated amount of interferon for the appropriate dose should be withdrawn from the vial(s), added to 100 mL of Sterile Normal Saline solution, and administered over 20 minutes. The final concentration of INTRON A[®] must not be less than 0.1 MIU/mL. **No other drug can be infused concomitantly with INTRON A[®].**

Compatibility with Other IV Fluids

In addition to IV normal saline solution, INTRON A[®] Lyophilized Powder, at final concentrations of 0.05 to one MIU per mL is stable and compatible in the following mixtures for up to 24 hours at refrigerated or at room temperature in glass bottles:

Ringers Injection	Lactate Ringers Injection
Amino Acid Injections	5% Sodium Bicarbonate Injection

INTRON A[®] Ready-to-Use Solution

Note: All vials containing INTRON A[®] Ready-to-Use Solution are provided with an overfill designed to take into consideration loss of solution in the needle/needle hub, thereby accommodating the appropriate prescribed dose to be withdrawn from the vial for injection.

For SC or IM administration: INTRON A[®] Ready-to-Use Solution (Albumin (human) free) may be injected directly after withdrawal of the appropriate doses from the vial with a sterile syringe.

For IV infusion: The infusion of INTRON A[®] Ready-to-use Solution (Albumin (human) free) should be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, the final concentration of interferon in normal saline must not be less than 0.3 MIU/mL. The appropriate dose should then be withdrawn from the vial(s), added to 50 mL of sterile normal saline solution in a PVC bag or glass bottle for intravenous use and administered over 20 minutes. The admixture is stable for at least 24 hours when stored between 2°C and 25°C. **No other drug can be infused concomitantly with INTRON A[®] Ready-to-Use Solution (albumin (human) free).**

As with all parenteral drug products, INTRON A[®] Injectable Solution should be inspected visually prior to administration. INTRON A[®] Injectable Solution is clear and colorless.

Compatibility with IV Administration Sets

The following IV drip sets can be considered compatible with the admixture containing INTRON A[®] Ready-to-Use-Solution (Albumin (human) free):

IV Administration Set	Product Code	Manufacturer
Venuset 78 Primary IV Set	1881	Abbott
Solution Administration Set	2C0001s	Travenol
Basic Solution Set w/5 µm filter	2c5455s	Baxter

INTRON A[®] Solution for Injection (Albumin (human) free), Multi-Dose Pen

INTRON A[®] Solution for Injection (Albumin (human) free), Multi-Dose Pen contains a pre-filled multi-dose cartridge for SC administration. It is designed to deliver fixed doses as required using a simple dial mechanism.

The needles provided in the packaging will be used for the INTRON A[®] Pen only. A new needle is to be used each time the pen delivers a dose. Each INTRON A[®] Pen is for an individual patient's use only.

The Multi-Dose Pen should be at room temperature (15 - 25°C) before administering each dose. The pen should be removed from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (15 - 25°C). After each use, the needle should be discarded safely and the pen must be returned to the refrigerator immediately (see ***STORAGE AND STABILITY*** section).

Table 1: Dosing Chart for INTRON A[®] Multi-Dose Pen

CLICKS	STRENGTH (MIU)		
	18 MIU PEN	30 MIU PEN	60 MIU PEN
1	0.3 MIU	0.5 MIU	1 MIU
2	0.6	1.0	2
3	0.9	1.5	3
4	1.2	2.0	4
5 (1 full turn)	1.5	2.5	5
6	1.8	3.0	6
7	2.1	3.5	7
8	2.4	4.0	8
9	2.7	4.5	9
10 (2 full turns)	3.0	5.0	10
11	3.3	5.5	11
12	3.6	6.0	12
13	3.9	6.5	13
14	4.2	7.0	14
15 (3 full turns)	4.5	7.5	15
16	4.8	8.0	16
17	5.1	8.5	17
18	5.4	9.0	18
19	5.7	9.5	19
20 (4 full turns – maximum)	6.0	10.0	20

Each Pen contains 1.5 mL of interferon alfa-2b solution: 1.2 mL for therapeutic use and 0.3 mL of extra solution added to clear air from the needle before injection.

As with all parenteral drug products, INTRON A[®] Injectable Solution should be inspected visually prior to administration. INTRON A[®] Injectable Solution is clear and colorless.

OVERDOSAGE

Symptoms and Treatment of Overdosage

Distinction between the therapeutic dose of INTRON A[®] and overdose has not been clearly defined. Symptoms of overdose may include amplification of the adverse effects, notably “flu-like” symptoms, leukopenia or thrombocytopenia and increased serum liver enzyme levels. The severity of the adverse reactions can be ameliorated by adjusting the dose level and schedule, or in some cases termination of INTRON A[®] therapy. CVS side effects such as hypotension and arrhythmia may require supportive therapy.

As for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient are indicated.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

INTRON A[®] 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*. INTRON A[®] also inhibits viral replication *in vitro* and *in vivo*.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. 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 immunomodulation activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. All of these activities possibly contribute to interferon's therapeutic effects.

Pharmacodynamics

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 ¹²⁵I-labelled interferon alfa-2b. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric and hydrophobic membrane proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity.

Alfa-2 interferon 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 antiproliferative activity of interferon alfa-2b was evaluated *in vitro* using mouse and human leukemia cell lines, and human osteosarcoma, melanoma, and normal amnion cells. The antiproliferative activity of interferon alfa-2b was most pronounced against human osteosarcoma cells and the human lymphocytic leukemia cell line RPMI-8402. Growth of both cell lines was inhibited 80 to 100% by interferon alfa-2b. No activity was seen in mouse leukemia cells, which again suggests species specificity.

The immunomodulating activity of interferon alfa-2b 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 1 histocompatibility antigens on the surface of a number of cells. These effects appear to be dose dependent.

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

Mixed results were obtained in the *in vivo* studies of antitumor activity of interferon alfa-2b. Intraperitoneal administration of interferon alfa-2b (0.1 to 1 MIU for 9 days) had no effect on the growth of human tumor xenografts in athymic mice or on murine leukemia cells implanted in BDF1 mice. Interferon alfa-2b injected intralesionally (0.2 or 0.8 MIU once daily for 7 days), however, delayed the development and reduced the volume of human osteosarcoma implants in athymic mice. The effect was dose related. Additionally, SC administration of interferon alfa-2b at a dose of 0.2 million units/day inhibited the growth of implanted human breast tumor xenografts in athymic mice by about 50% after 23 days.

A human tumor stem cell assay was used to study the effects of recombinant interferon alfa-2b in combination with doxorubicin. Study results indicated that a schedule dependent synergistic effect was exhibited when doxorubicin and recombinant interferon alfa-2b were combined in the cell lines tested. Antagonistic effects or cell growth enhancement over control levels were not observed.

Preliminary studies with isolated and perfused rabbit kidneys have shown that the kidney may be the main site of interferon alpha catabolism.

Pharmacokinetics

The pharmacokinetics of INTRON A[®] were studied in 12 healthy male volunteers following single doses of 5 MIU/m² administered intramuscularly, subcutaneously and as a 30 minute IV infusion in a cross-over design. Interferon concentrations were determined using a radioimmunoassay (RIA) with a detection limit equal to 10 IU/mL. The mean serum interferon concentrations following IM and SC 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 interferon following both IM and SC injections were approximately two to three hours. Serum levels were below the detection limit 16 hours post-injection. After IV administration, serum interferon levels peaked (135 to 273 IU/mL) by the end of the infusion, then declined at a slightly more rapid rate than after SC or IM drug administration, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours. Urine levels of interferon following a single dose (5 MIU/m²) were below the detection limit following each of the three routes of administration.

In another study, the pharmacokinetics of INTRON A[®] were studied in 12 healthy male volunteers following single 10 MIU doses administered subcutaneously, intramuscularly and as a 30 minute IV infusion. The mean serum level profiles of interferon following SC and IM injections were comparable. The maximum serum levels obtained at six to eight hours after injection were approximately 150 - 180 IU/mL. The elimination half-lives of interferon following both SC and IM injections were approximately six to seven hours. Serum levels were below the detection limit of 25 IU/mL, 24 hours after the injections. Serum levels of interferon after IV administration peaked (546 IU/mL) by the end of the infusion, then declined rapidly with time, becoming undetectable four hours after the infusion. Urine levels of interferon were below the detection limit following each of the three routes of administration.

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

Serum Anti-Interferon Neutralizing Antibodies: Interferon neutralizing factor assays were performed on serum samples of patients who received INTRON A[®] in monitored clinical trials. The clinical incidence of neutralizing activity developing in cancer patients treated systemically is approximately 3%, and in chronic hepatitis patients is 6.2% with no loss of response due to the low titers.

Serum interferon neutralizing activity was detected in approximately 1% of patients who received INTRON A[®] intralesionally for condylomata acuminata. The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. No development of neutralizing antibodies has been demonstrated in patients who received INTRON A[®] intralesionally in the treatment of basal cell carcinoma or in patients who received INTRON A[®] intravesically in the treatment of bladder cancer.

Serum anti-interferon neutralizing antibodies were detected in 15% (9/58) of the patients who received INTRON A[®] for chronic hepatitis C at 3 MIU three times per week for 6 months and were tested for antibody activity. The titers detected were low in all patients and had no discernible effect on the course of disease or the response to interferon treatment.

Serum anti-interferon neutralizing antibodies were detected in 7% (6/85) of the patients who received INTRON A[®] therapy for chronic hepatitis B at 5 MIU daily for 4 months and in 3% (1/38) of patients treated at 10 MIU, three times per week. The titers were low and did not appear to affect efficacy. The significance of the appearance of serum neutralizing activity is not known.

STORAGE AND STABILITY

Stability and Storage Recommendations

Store lyophilized powder, Ready-to-Use Solution, and Multi-Dose Pen between 2 - 8°C. INTRON A[®] should not be frozen. Do not use past expiry date on labels.

INTRON A Lyophilized Powder

Before reconstitution, INTRON A[®] should be stored in the refrigerator between 2°C and 8°C. For the purpose of transport and/or to facilitate ambulatory use, the non-reconstituted product can be kept at room temperature (up to 25°C) for a period up to four weeks before use. If the product is not reconstituted during the four-week period, it cannot be put back in the refrigerator for a new storage period and should be discarded.

Reconstituted lyophilized INTRON A[®] diluted with Sterile Water for Injection USP - supplied with INTRON A[®]:

After reconstitution with Sterile Water for Injection, the product is to be used immediately. Since no preservative is present, it is recommended that administration of the solution occur as soon as possible and within 3 hours of reconstitution. For reconstitution under controlled and validated aseptic conditions such as a hospital pharmacy, the chemical and physical in-use stability for the reconstituted solution has been demonstrated 24 hours at 2 - 8°C. Discard any unused portion.

INTRON A[®] Ready-to-Use-Solution (Albumin (human) free)

10 MIU vials: After first use, any unused solution is stable for 7 days maximum when refrigerated at 2 - 8°C.

18 and 25 MIU vials: After first use, the solution is stable four weeks maximum when refrigerated at 2 - 8°C. Any solution remaining after four weeks must be discarded.

For the purpose of transport and/or to facilitate ambulatory use, the solution can be kept at room temperature (up to 25°C) for a period up to seven days before use. INTRON A[®] Ready-to-Use Solution (Albumin (human) free) can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and should be discarded.

INTRON A[®] Solution for Injection (Albumin (human) free), Multi-Dose Pen

Refrigerate at 2 - 8°C. Each pen is intended for a maximum four-week use period and then must be discarded. A new needle must be used for each dose. After each use, the needle should be discarded safely, and the pen must be returned to the refrigerator immediately. In case the product is left inadvertently at room temperature (15 - 25°C), a maximum total of 48 hours (two days) of exposure at room temperature (15 - 25°C) is permitted over the four-week use period.

No other drug can be infused concomitantly with INTRON A[®].

DOSAGE FORMS, COMPOSITION AND PACKAGING

Lyophilized Powder with Diluent:

10 MIU interferon alfa-2b/vial

18 MIU interferon alfa-2b/vial

Each vial of lyophilized powder is packaged with 1 vial of diluent containing 1 mL sterile water.

Ready-to-Use Solution (Albumin (human) free):

10 MIU interferon alfa-2b/vial (10 MIU/mL)

18 MIU interferon alfa-2b/vial (6 MIU/mL)

25 MIU interferon alfa-2b/vial (10 MIU/mL)

Solution for Injection (Albumin (human) free), Multi-Dose Pen:

18 MIU interferon alfa-2b/pen (15 MIU/mL)

30 MIU interferon alfa-2b/pen (25 MIU/mL)

60-MIU interferon alfa-2b/pen (50 MIU/mL)

Each pre-filled pen is packaged with 12 NOVOFINE^{*} 30G 8mm needles and alcohol swabs.

Composition

INTRON A[®] Lyophilized Powder with Diluent: Each vial contains 10 or 18 MIU of interferon alfa-2b, 20 mg aminoacetic acid, 2.27 mg sodium phosphate dibasic anhydrous, 0.55 mg sodium phosphate monobasic monohydrate, 1 mg albumin (human).

Each vial of lyophilized powder is packaged with 1 vial of diluent containing 1 mL sterile water for injection.

INTRON A[®] Ready-to-Use Solution (Albumin (human) free): In vials containing 18 MIU of interferon alfa-2b, in which each mL contains 6 MIU of interferon alfa-2b and in vials containing 10 or 25 MIU of interferon alfa-2b, in which each mL contains 10 MIU of interferon alfa-2b. Each mL also contains 0.1 mg edetate disodium, 1.5 mg m-cresol, 0.1 mg polysorbate 80, 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic anhydrous, 1.3 mg sodium phosphate monobasic monohydrate, q.s. Water for Injection to make 1.0 mL.

INTRON A[®] Solution for Injection (Albumin (human) free), Multi-Dose Pen: In glass carpoules containing 18 MIU (15 MIU/mL), 30 MIU (25 MIU/mL) or 60 MIU (50 MIU/mL) of interferon alfa-2b. Each mL also contains 0.1 mg edetate disodium, 1.5 mg m-cresol, 0.1 mg polysorbate 80, 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic anhydrous, 1.3 mg sodium phosphate monobasic monohydrate, q.s. Water for Injection to make 1 mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

The activity of interferon alfa-2b is expressed in terms of International Units (IU), with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6×10^8 IU. International Units are determined by comparison of the activity of the recombinant interferon alfa-2b with the activity of the international reference preparation of human leukocyte interferon established by the World Health Organization.

Drug Substance

Proper name:
interferon alfa-2b

Molecular formula:

(as deduced from the nucleotide sequence of cDNA)

CYS ASP LEU PRO GLN THR HIS SER LEU GLY SER ARG ARG THR LEU MET
LEU LEU ALA GLN MET ARG ARG ILE SER LEU PHE SER CYS LEU LYS ASP
ARG HIS ASP PHE GLY PHE PRO GLN GLU GLU PHE GLY ASN GLN PHE GLN
LYS ALA GLU THR ILE PRO VAL LEU HIS GLU MET ILE GLN GLN ILE PHE
ASN LEU PHE SER THR LYS ASP SER SER ALA ALA TRP ASP GLU THR LEU
LEU ASP LYS PHE TYR THR GLU LEU TYR GLN GLN LEU ASN ASP LEU GLU
ALA CYS VAL ILE GLN GLY VAL GLY VAL THR GLU THR PRO LEU MET LYS
GLU ASP SER ILE LEU ALA VAL ARG LYS TYR PHE GLN ARG ILE THR LEU
TYR LEU LYS GLU ASP LYS TYR SER PRO CYS ALA TRP GLU VAL VAL ARG
ALA GLU ILE MET ARG SER PHE SER LEU SER THR ASN LEU GLN GLU SER
LEU ARG SER LYS GLU

Molecular mass:
approximately 19,300 daltons

TOXICOLOGY

Interferons are generally recognized to show species specificity. Nevertheless, toxicology studies in mice, rats and monkeys were conducted. Injections of human interferon alfa-2b for up to three months revealed no evidence of systemic toxicity in these species.

Tolerance of intranasally administered human interferon alfa-2b was evaluated in beagle dogs. No clinical signs of toxicity were observed during a 13 day observation period following one day's treatment with a total dose of 45 MIU of human interferon alfa-2b.

Results of animal reproduction studies indicate that recombinant interferon alfa-2b was not teratogenic in rats or rabbits, nor did it adversely affect pregnancy, fetal development or reproductive capacity in offspring of treated rats. Furthermore, animal studies have shown that interferons do not cross the placental barrier.

Interferon has been shown to have abortifacient effects in rhesus monkeys (*Macaca mulatta*) at 90 and 180 times the IM or SC dose of 2 MIU/m². Although abortion was observed in all dose groups (7.5, 15 and 30 MIU/kg), it was only statistically significant versus control at the mid-and high-dose groups (corresponding to 90 and 180 times the IM or SC dose of 2 MIU/m²).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Interferon may impair fertility. In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed. Decreases in serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

Studies with interferon alfa-2b have not been performed to determine carcinogenicity.

Mutagenicity studies with interferon alfa-2b revealed no adverse effects.

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PART III: CONSUMER INFORMATION



This leaflet is part III of a three-part "Product Monograph" published when INTRON A[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INTRON A[®]. Contact your doctor or pharmacist if you have any questions about the drug.

Before using INTRON A[®] (interferon alfa-2b), you should read the following information and carefully follow the instructions.

ABOUT THIS MEDICATION

What the medication is used for:

INTRON A[®] can be used to treat the following diseases:

- Chronic Hepatitis C;
- Chronic Active Hepatitis B;
- Chronic Myelogenous Leukemia (CML), and thrombocytosis associated with CML;
- Multiple Myeloma;
- Non-Hodgkin's Lymphoma;
- Malignant Melanoma;
- AIDS-Related Kaposi's Sarcoma;
- Hairy Cell Leukemia;
- Basal Cell Carcinoma;
- Condylomata Acuminata.

What it does:

Interferons are among a number of substances produced in response to the presence of enemy cells. Not only do they "interfere" with foreign invaders that may cause infection, but they can prevent the growth and spread of other diseased cells as well, including some types of cancer cells. INTRON A[®] is a synthetic man-made version of these substances.

When it should not be used:

- If you are hypersensitive (allergic) to this drug, to any ingredient in the formulation or component of the container or to any interferon.
- If you have severe kidney disease.
- If you have autoimmune hepatitis (hepatitis caused by your immune system attacking your liver) or unstable liver disease (yellowing of the skin and eyes, swelling of the abdomen).

What the medicinal ingredient is:

The medicinal ingredient is interferon alfa-2b.

What the important nonmedicinal ingredients are:

For a full listing of nonmedicinal ingredients see Part 1 of the

product monograph. You may also refer to the INTRON A[®] label.

What dosage forms it comes in:

- Lyophilized Powder with Diluent;
- Ready-to-Use Solution; and
- Solution for Injection, Multi-Dose Pen.

WARNINGS AND PRECAUTIONS

BEFORE you use INTRON A[®] talk to your doctor or pharmacist if:

- you have an infectious disorder;
- you had a heart attack, or have other heart problems;
- you have kidney problems;
- you have liver problems;
- you have nervous or mental problems (such as depression);
- you have had a body organ transplant;
- you have thyroid disease;
- you have problems with your immune system;
- you have diabetes or high blood pressure (your doctor may ask you to have periodic eye examinations);
- you have high blood fat levels (such as elevated triglycerides or cholesterol levels).
- you have psoriasis or sarcoidosis;
- you have symptoms of colitis (abdominal pain, bloody diarrhea, fever);
- you have respiratory symptoms (fever, cough, dyspnea);
- you are taking the Chinese herbal medication *Shosaikoto* (also known as *Xiao-Chai-Hu-Tang*);
- you have a history of substance abuse (e.g., alcohol or drugs);
- you think you are pregnant, are thinking of becoming pregnant or are breast-feeding. If you are prescribed INTRON A[®] in combination with ribavirin, ribavirin causes serious birth defects or fetal death, thus both female and male patients must use effective contraception if there is any chance for pregnancy to occur.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with INTRON A[®] include:

- anticancer drugs.

Tell your doctor or pharmacist if you are taking SEBIVO* (telbivudine) for chronic hepatitis B because taking this medicine together with INTRON A[®] may increase your risk of developing peripheral neuropathy (numbness, weakness, tingling, and/or burning sensations, or pain in the arms and/or legs). The combined use of these medications is not recommended.

PROPER USE OF THIS MEDICATION

If you are using the INTRON A[®] Ready-to-Use Solution in vials, see the *Use of the INTRON A[®] Ready-to-Use Solution (Albumin (human) free)*-section.

If you are using the INTRON A[®] Pen, see the *Use of the INTRON A[®] Solution for Injection (Albumin (human) free), Multi-Dose Pen* section.

Use of the INTRON A[®] Lyophilized Powder

To prepare INTRON A[®] solution:

1. With pencil or pen, write the discard date in the space provided on the label; see the *How to Store it* section for the length of time that the solution may be stored before discarding. Do not use after expiration date.
2. Wash your hands thoroughly with soap and water, rinse, and towel dry.
3. Remove the protective plastic cap from the top of both the diluent and INTRON A[®] vial, leaving the rubber stopper and aluminium ring in place.
4. Clean the rubber stopper on the top of each vial with an alcohol swab. Your physician will tell you what size syringe and needle to use for mixing and how much diluent to add to the INTRON A[®] vial.
5. Remove the protective cap from the syringe needle and fill with air by pulling the plunger to the volume of diluent to be added.
6. Hold the diluent upright without touching the-cleaned top of the vial with your hands.
7. Insert the needle into the vial containing the diluent and inject the air into the vial.
8. Invert the vial and make sure that the top of the needle is in the liquid.
9. Withdraw the diluent to be added to the INTRON A[®] vial by pulling the plunger to the exact amount your physician has told you. The marks on the side of the syringe indicate the amount of diluent withdrawn. Withdraw the needle from the vial. Gently tap syringe to clear air bubbles. Gently push plunger to get rid of air from end of syringe.
10. To prepare the INTRON A[®] solution, insert the needle through the rubber top of the INTRON A[®] vial and gently place the needle top against the glass wall of the vial.

11. Slowly inject the diluent, aiming the stream of liquid at the glass wall of the vial in order to avoid production of air bubbles.

12. Do not aim the stream at the white powder at the bottom of the vial.

13. Remove needle, replace needle cap on needle and place syringe on a flat surface.

14. To dissolve the white contents, swirl the vial of INTRON A[®] with a gentle rotatory motion until the contents are completely dissolved. **Do not shake vial.**

15. If air bubbles do form, wait until the solution has settled and all bubbles have risen to the top of the solution and disappeared before injecting the dose. The reconstituted solution is clear and colorless to light yellow in color.

Refer to the *Administration of INTRON A[®]* section for instructions on administering INTRON A[®].

Use of the INTRON A[®] Ready-to-Use Solution (Albumin (human) free)

1. With pencil or pen, write the discard date in the space provided on the label; see the *How to Store it* section for the length of time that the solution may be stored before discarding.
2. Check solution for change in color, cloudiness, and expiry date.
3. Leave vial at room temperature for ten minutes. Do not shake.
4. Wash your hands thoroughly with soap and water, rinse, and towel dry.
5. Remove the protective plastic cap from vial, leaving the rubber stopper and aluminium ring in place, and discard.

Refer to the *Administration of INTRON A[®]* section for instructions on administering INTRON A[®].

Administration of INTRON A[®]
Filling the Syringe with INTRON A[®]



- Wipe top of vial with an alcohol swab.

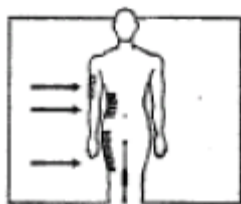
- If syringe is cracked, or needle is bent-put into disposable bottle.
 - Pull needle cap straight off. Fill syringe with air by pulling the plunger to the volume of INTRON A[®] to be withdrawn.
 - With vial on flat surface, push needle through rubber stopper of INTRON A[®] vial and inject the air into the vial.
 - With needle in vial, turn vial upside down making sure needle is in solution.
 - Pull back plunger and slowly withdraw prescribed amount of solution into syringe. Check dose again.
- (Note: It may be possible to withdraw greater than the prescribed amount of INTRON A[®] for injection from the vial. Withdraw only the prescribed amount)-
- Remove needle from vial. Keep needle end up. Do not touch needle. Gently tap syringe to clear air bubbles. Gently push plunger to get rid of air from end of syringe.
 - Replace the cover on the needle and put the syringe on a clean flat surface.

Selecting an Injection Site for subcutaneous injection

- Do not inject in area that is red or sore.
- Use the same site only once every six or seven weeks.

Injection sites:

Thighs, outer surface of upper arms, abdomen-except navel or below waistline.



Preparing to inject



- Using a circular motion, clean site with an alcohol swab (approximately for 10 seconds). Allow area to dry. (6)
- Remove the needle cap.
- Hold syringe between thumb and forefinger-like holding a pencil.
- With other hand grab skin where injection will be made.
- Hold needle at a 45 to 90 degree angle to the skin about 2 inches (5 cm) above the skin surface, insert the needle with a quick jab as if throwing a dart. The entire needle or at least 3/4 of it should go into the skin. (7)
- Pull back on plunger 1/4 of an inch. If you see blood in the syringe, do not inject. Withdraw and discard the syringe, prepare a new syringe and inject at a new site. If you do not

- see blood in the syringe, slowly push the plunger to inject the INTRON A[®]. (8)
- After injecting solution, pull out needle. Put alcohol swab over site for a few seconds. Do not press down. (9)
- If needed, put on bandaid.

Cleaning up

- Do not put cover back on needle.
- Place empty syringe with needle in disposal bottle. Check with your nurse or pharmacist for proper disposal.

Intramuscular injection:

- INTRON A[®] may be administered intramuscularly providing you are taught by your doctor to administer by this route.

Use of the INTRON A[®] Solution for Injection (Albumin (human) free), Multi-Dose Pen

The INTRON A[®] Solution for Injection (Albumin (human) free), Multi-Dose Pen is a pre-filled, ready-to-use dial-a-dose syringe that contains INTRON A[®] solution. This Multi-Dose Pen is designed to deliver six to twelve doses of INTRON A[®] with improved injection comfort. If necessary the pen can be adjusted to give different doses (i.e. if your doctor wants you to increase or decrease your dose).

Please note the following important points before using your INTRON A[®] Injection Pen:

The INTRON A[®] Injection Pen should **only** be used with the enclosed NOVOFINE* 30G 8mm needles. The use of other needles may result in the pen not working properly and/or in the wrong dose of INTRON A[®] being delivered.

Always discard needles and used pens carefully; **never** discard the pen with the needle attached.

Use the INTRON A[®] Injection Pen **only** in accordance with these instructions. **Do not** allow the INTRON A[®] Injection Pen to be handled roughly or otherwise misused.

Keep out of reach of children.

How to Use your INTRON A[®] Injection Pen:

The Pen should be at room temperature (15 - 25°C) before administering each dose. The Pen should be removed from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (15 - 25°C).

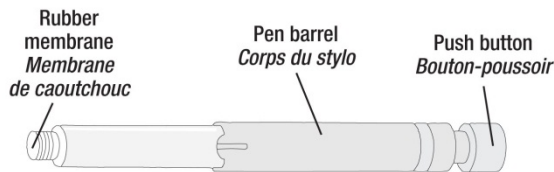
Always check that INTRON A[®] solution is clear in appearance prior to use. If it does not have a clear

uniform appearance, **do not use**. Please consult your physician or pharmacist.

When you are ready to give your injection, prepare your pen as follows:

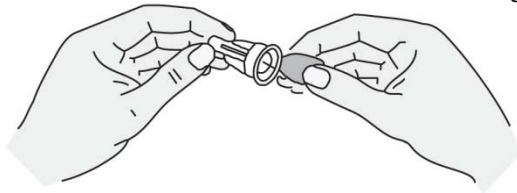
1. First check that you have the correct INTRON A® Injection Pen as prescribed by your doctor. There are three kinds; each one has a different color push button indicating the maximum dosage.
2. Wash your hands thoroughly with soap and water, rinse, and towel dry.
3. Pull off the cap of the pen and disinfect the rubber membrane with one alcohol wipe (Diagram A).

Diagram A



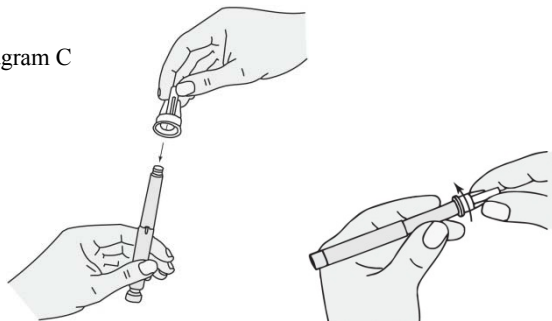
4. Remove the protective tab from the NOVOFINE® needle. Note that once the protective tab is removed, the rear portion of the needle is revealed (Diagram B).

Diagram B



5. Gently push the NOVOFINE® needle onto the Pen as shown in Diagram C. (Notice that the rear portion of the needle described in the previous step will pierce through the rubber membrane that you disinfected previously.) Screw the needle onto the INTRON A® Pen by securely turning it in a clockwise direction.

Diagram C



6. Pull off the outer needle cap (Diagram D). Next, pull off the inner needle cap carefully, bearing in mind that the needle point will now be exposed (Diagram E). Keep the outer needle cap nearby for later use. Because a small amount of air may collect in the needle and reservoir during storage, the next step is to remove any air bubbles. This is called “performing the air-shot”.

Diagram D

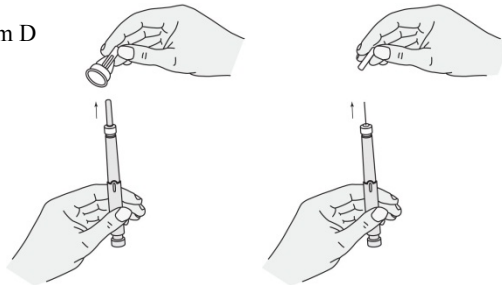


Diagram E

7. Hold the INTRON A® Injection Pen with the needle pointed upward.

8. Tap the reservoir with your finger so that any air bubbles rise to the top of the reservoir, just below the needle (Diagram F).



Diagram F

9. Hold the pen by the barrel and turn the reservoir in the direction indicated by the arrow in Diagram G (clockwise) until you feel it click.

Diagram G



10. Keeping the pen pointing upward, press the push button up full and see if a drop of INTRON A® appears at the needle tip (Diagram H).

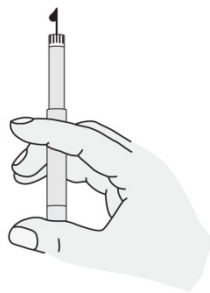


Diagram H

If no drop appears, then repeat the previous two steps until a drop appears at the needle tip.**

11. Replace the INTRON A® Injection Pen cap with the triangle opposite the dosage indicator, as seen in Diagram I. The pen is now ready to set the dose. For the next step, hold the pen at the middle of the barrel. This will allow the push button to move freely, ensuring that the correct dose is set.

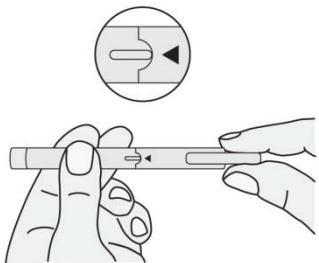


Diagram I

12. To set the required dose, hold the pen horizontally by the barrel with one hand. With the other hand, turn the cap in a clockwise direction indicated by the arrow (Diagram J). You will observe the push button rising, indicating the dose set (Diagram K). Check that you have the correct dose.

Diagram J

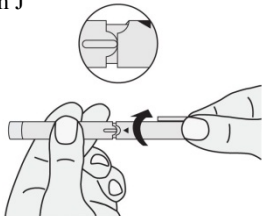
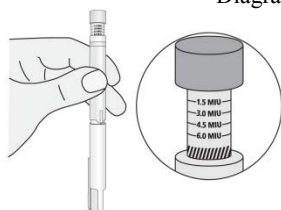
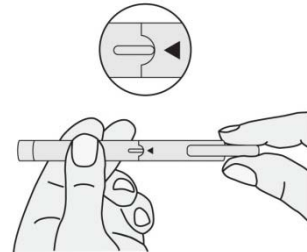


Diagram K

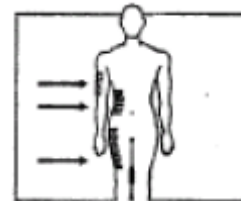


13. After each complete turn, make sure that the triangle is opposite to the dosage indicator (Diagram L). If you have set a wrong dose, simply turn the cap back (counter-clockwise) as far as you can until the push button is fully home, and start again. Once the correct dose is set, you are ready to give the injection.

Diagram L

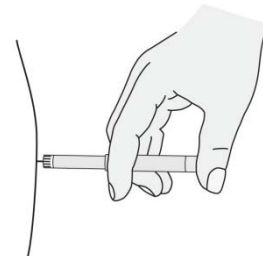


14. Do not inject in area that is red or sore. Use the same site only once every six or seven weeks. Injection sites: Thighs, outer surface of upper arms, abdomen—except navel or below waistline. Using a circular motion, clean the site with an alcohol swab (approximately for 10 seconds). Allow area to dry.



15. Remove the pen cap and insert the needle as you have been shown by your doctor or nurse. Press the push button down fully (Diagram M).

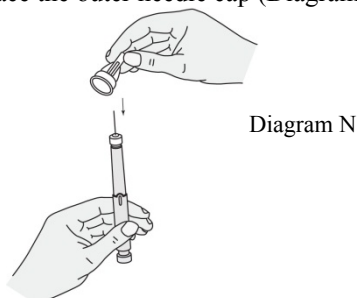
Diagram M



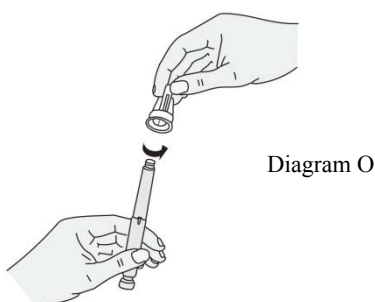
16. Leave the needle in place for a few seconds to allow the INTRON A® to distribute under the skin, then remove.

** **Note:** Even after the “air-shot”, some air may remain in the pen, but this is not important as you have removed the air from the needle and the dose will be accurate.

17. Carefully replace the outer needle cap (Diagram N).

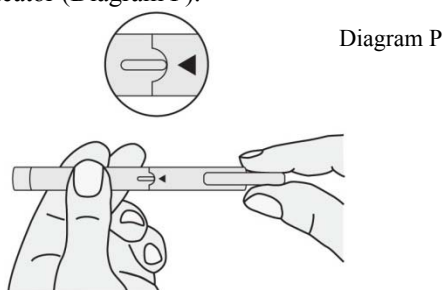


18. Completely unscrew the needle assembly using a counter-clockwise motion (Diagram O).



19. Next carefully lift it off the pen and discard the capped needle (Diagram O).

20. Replace the pen cap with the triangle once again opposite the dosage indicator (Diagram P).



Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you are self-administering treatment, or if you are the caregiver, inject the recommended dose as soon as you remember and continue treatment as usual. Do not take a double dose to make up for a forgotten dose. If you are scheduled to inject this product every day, and you accidentally missed a full day's dose, continue treatment at the usual dose the following day. Contact your doctor or pharmacist if needed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, INTRON A[®] can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

Contact your doctor immediately if you have a severe allergic reaction (which may include swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; wheezing, hives or fainting). Cases of acute hypersensitivity reactions have been reported.

The most frequently reported side effects, especially at the beginning of treatment with INTRON A[®], have been fever, fatigue, headache and muscle aches joint pain and chills/rigors (flu-like symptoms). Your doctor may recommend you take acetaminophen if you develop these symptoms. Fever and fatigue have been reversible within 72 hours of interruption or cessation of treatment and were dose related. While fever may be related to these "flu-like" symptoms, other causes of persistent fever should be excluded.

Check with your doctor immediately if any of the following side effects occur:

- chest pain or persistent and severe cough
- irregular or rapid heartbeat
- breathing problems (including shortness of breath)
- confusion
- altered mental status
- feeling depressed or wanting to harm yourself (suicidal thoughts or attempts)
- hallucinations
- changed behaviour or aggressive behaviour (sometimes directed against others)
- nervousness or agitation
- numbness or tingling feeling or pain in hands or feet
- dizziness
- impaired consciousness or loss of consciousness
- convulsion ("seizure or fit")
- trouble sleeping, thinking or concentrating or difficulty remaining alert
- severe stomach pain or cramps
- blood or clots in stool (or black, tarry stool)
- fever or chills beginning after a few weeks of treatment
- nausea and vomiting
- diarrhea or constipation
- severe nosebleed
- waxy pallor

- pain in your lower back or side
- muscle pain or joint pain (sometimes severe)
- difficulty or inability to pass urine
- feeling tired (low thyroid gland activity)
- high sugar level in blood
- problems with your eyes or your eyesight or hearing, loss of hearing
- bleeding gums (periodontal) or dental disorders
- loss of appetite or taste alteration
- severe or painful reddening of your skin or mucous membrane

Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Tell your doctor as soon as possible if you have any of the following side effects (medical attention may be required):

Very commonly reported side effects (at least 1 in every 10 patients):

Pain, swelling and redness or skin damage at site of injection, hair loss, dizziness, changes in appetite, stomach or abdominal pains, diarrhea, nausea (feeling sick), viral infection, depression, emotional lability, insomnia, anxiety, sore throat and painful swallowing, fatigue, chills/rigors, fever, flu-like reaction, feeling of general discomfort, headaches, weight loss, vomiting, irritability, weakness, mood swings, coughing (sometimes severe), shortness of breath, itching, dry skin, rash, sudden and severe muscle pain, joint pain, musculoskeletal pain, and changes in laboratory blood values including decreased white blood cell count.

Commonly reported side effects (at least 1 in every 100 patients, but less than 1 in every 10 patients):

Thirst, dehydration, high blood pressure, migraines, swollen glands, flushing, menstrual problems, decreased sexual drive, vaginal problem, breast pain, pain in testicle, problems with thyroid gland, red gums, dry mouth, red or sore mouth or tongue, tooth ache or tooth disorder, herpes simplex (fever blisters), taste change, upset stomach, dyspepsia (heartburn), constipation, enlargement of liver (liver problems, sometimes severe), loose stools, bedwetting in children, inflammation of the sinuses, bronchitis, eye pain, problem with your tear ducts, conjunctivitis ("pink eye"), agitation, sleepiness, sleepwalking, problem with behaviour, nervousness, stuffy or runny nose, sneezing, rapid breathing, pale or reddened skin, bruising, fingers and toes very sensitive to cold, problem with skin or nails, psoriasis (new or worsened), increased sweating, increased need to pass urine, fine shaking movements, decreased sensitivity to touch, and arthritis.

Rarely reported side effects (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):

Pneumonia and new or worse high blood pressure in the lungs (pulmonary hypertension)

Very rarely reported side effects (less than 1 in every 10,000 patients):

Low blood pressure, puffy face, diabetes, leg cramps, back pain, kidney problems, nerve damage, bleeding gums, aplastic anemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anemia, symptoms of which would include unusual tiredness and a lack of energy.

Very rarely sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported.

Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about killing others, and blindness have been reported with INTRON A[®] use.

Other side effects not listed above may also occur in some patients. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking INTRON A[®], contact your doctor or pharmacist.

HOW TO STORE IT

INTRON A[®] Lyophilized Powder

Before reconstitution^a, INTRON A[®] should be stored in the refrigerator at 2°C to 8°C. For the purpose of transport, the non-reconstituted product can be kept at room temperature (up to 25°C) for a period up to four weeks before use. If the product is not reconstituted during the four-week period, it cannot be put back in the refrigerator for a new storage period and should be discarded.

Upon reconstitution with Sterile Water for Injection, the solution is clear and colorless to light yellow in color.

^a Reconstituting means adding a liquid (diluent) to a dry powder.

The solution must be used immediately; although not recommended, it may be stored for 24 hours at 2°C to 8°C.

Unused portion should be discarded.

INTRON A[®] should not be frozen.

INTRON A[®] Ready-to-Use-Solution (Albumin (human) free)

- 10 million IU vials: After first use, any unused solution is stable for 7 days maximum when refrigerated at 2 - 8°C
 - 18 and 25 million IU vials: After first use, the solution is stable four weeks maximum when refrigerated at 2 - 8°C.
 Any solution remaining after four weeks must be discarded.

For the purpose of transport, the solution can be kept at room temperature (up to 25°C) for a period up to seven days before use. INTRON A[®] Ready-to-Use Solution (Albumin (human) free) can be put back in the refrigerator at any time during this seven-day period. If the product is not used during the seven-day period, it cannot be put back in the refrigerator for a new storage period and should be discarded.

INTRON A[®] Injectable Solution is clear and colorless.

INTRON A[®] should not be frozen. **Frozen storage of the filled syringes is not recommended.**

Use of the INTRON A[®] Solution for Injection (Albumin (human) free), Multi-Dose Pen

When the INTRON A[®] Injection Pen is not in use, you should store it in the refrigerator at 2 - 8°C. Each pen is for a four-week use period and then must be discarded. A new needle must be used for each dose. After each use, the needle should be discarded safely, and the pen must be returned to the refrigerator immediately. In case the product is left inadvertently at room temperature (15 - 25°C), a maximum total of 48 hours (two days) of exposure at room temperature (15 - 25°C) is permitted over the four-week use period.

INTRON A[®] Injectable Solution is clear and colorless.

INTRON A[®] should not be frozen.

Always check the expiration date; never use after the expiration date.

REPORTING SIDE EFFECTS

You can help improve the safe use of Health Products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: **Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9**

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about INTRON A[®]:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information (or Consumer Information) by visiting the Health Canada website or Merck Canada website www.merck.ca or by calling Merck Canada at 1-800-567-2594

To report an adverse event related to INTRON A[®], please contact 1-800-567-2594.

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