

NEW ZEALAND DATA SHEET

INTRON® A

NAME OF DRUG

Interferon alfa-2b (rbe)

DESCRIPTION

INTRON A is a sterile, stable formulation of highly purified interferon alfa-2b produced by recombinant DNA techniques. Recombinant interferon alfa-2b is a water soluble protein with a molecular weight of approximately 19,300 daltons. It is obtained from a clone of *E. coli* which has a genetically engineered plasmid containing an interferon alfa-2 gene from human leucocytes.

The activity of INTRON A is expressed in terms of International Units (IU). The specific activity of INTRON A is approximately 2.6×10^8 IU/mg protein.

PRESENTATION

INTRON A Injectable (HSA-free) Solution

INTRON A HSA-free Injectable Solution is a clear, colourless solution and is presented in a single dose vial. Each vial of INTRON A HSA-free Injectable Solution contains either 10 million IU/1 mL, 18 million IU/3 mL or 25 million IU/2.5 mL of recombinant interferon alfa-2b. The vials also contain sodium phosphate dibasic, sodium phosphate monobasic, disodium edetate, sodium chloride, polysorbate 80, water for injections and m-cresol as preservative.

PHARMACOLOGY

Interferons are a family of naturally occurring, small protein molecules produced and secreted by cells in response to viral infections or various synthetic and biological inducers.

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

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

Recombinant interferon alfa-2b has exhibited antiproliferative effects in preclinical studies employing both cell culture systems and human tumour xenografts in animals, and has demonstrated significant immunomodulatory activity *in vitro*. Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*.

The antiproliferative activity of recombinant interferon alfa-2b was evaluated *in vitro* using mouse and human leukaemia cell lines, and human osteosarcoma, melanoma, and normal amnion cells. The antiproliferative activity of recombinant interferon alfa-2b was most

pronounced against human osteosarcoma cells and the human lymphocytic leukaemia cell line RPMI-8402; growth of both cell lines was inhibited 80-100%. No activity was seen in mouse leukaemia cells, which again suggests species specificity.

The immunomodulating activity of recombinant 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 tumour cells and its induction of Class I histocompatibility antigens on the surface of a number of cell types. These effects appear to be dose-dependent.

Subcutaneous administration of recombinant interferon alfa-2b at a dose of 0.2 million IU/day inhibited the growth of implanted human breast tumour xenografts in athymic mice by about 50% after 23 days. However, intra-peritoneal administration of recombinant interferon alfa-2b (0.1 - 1 million IU for 9 days) demonstrated no effect on the growth of human tumour xenografts in athymic mice or on murine leukaemia cells implanted in BDF1 mice.

A human tumour stem cell assay was used to study the effects of recombinant interferon alfa-2b in combination with doxorubicin. Study results suggested 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 alfa catabolism.

Clinical Trials

Kaposi's Sarcoma: In patients with AIDS-related Kaposi's sarcoma, measures of immunologic competence, commonly characterised by the baseline T4 count or T4/T8 ratio, have been noted to be highly predictive of the status of AIDS patients and their likelihood of response to INTRON A treatment. In patients with baseline T4 counts above 400, the overall response rate to INTRON A can be expected to be as high as 78%. Few patients with baseline T4 counts less than 200 can be expected to respond to INTRON A.

Chronic hepatitis B: Studies in patients with compensated liver disease and evidence of chronic hepatitis B virus infection (serum HBsAg positive) and HBV replication (serum HBeAg positive and serum HBV-DNA positive) have demonstrated that INTRON A therapy can produce virological remission of this disease (loss of serum HBeAg) and normalisation of serum aminotransferases.

In clinical studies, 39% (15/38) of responding patients lost HBeAg 1 to 6 months following the end of INTRON A therapy. Virological response was associated with a reduction in serum ALT to normal or near normal (≤ 1.5 times the upper limit of normal) in 87% (13/15) of patients responding to INTRON A therapy at 5 million IU daily. Of responding patients who lost HBsAg, 58% (7/12) did so 1 to 6 months post-treatment.

Chronic hepatitis C: Studies in patients with compensated liver disease and a history of blood or blood product exposure and/or positive HCV antibody demonstrated that INTRON A therapy can produce clinically meaningful effects on this disease, manifested by normalisation of serum ALT and reduction in liver necrosis and degeneration.

A multicentre study comparing treatment of chronic hepatitis C using INTRON A (i) 3 million IU three times weekly for a duration of 18 months, (ii) 3 million IU three times weekly for 6 months then 1 million IU three times weekly for 12 months and (iii) 3 million IU three times weekly for 6 months showed that treatment with 3 million IU three times weekly for a duration of 18 months produced significantly superior histological improvement, virological response and sustained ALT response than the regimens involving a lower dose or shorter duration of treatment.

Similarly, an Australian multicentre study evaluated the efficacy of INTRON A (i) 3 million IU three times weekly for 6 months, (ii) 5 million IU three times weekly for 6 months and (iii) 3 million IU three times weekly for 24 months. Treatment for a duration of up to 24 months

significantly improved the sustained response in patients who achieved normalisation of ALT at 24 weeks of therapy compared to the two 6-month treatment regimens. Sustained ALT response was associated with virological response and improvement in hepatic inflammation. This study confirmed that INTRON A 3 million IU three times weekly remains the optimal dose; increasing the dose to 5 million IU three times weekly did not significantly improve the ALT response rate or sustained ALT response.

Malignant melanoma: The safety and efficacy of INTRON A was evaluated as adjuvant to surgical treatment in patients with melanoma who were free of disease (post-surgery) but at high risk for systemic recurrence. These included patients with lesions of Breslow thickness >4 mm, or patients with lesions of any Breslow thickness with primary or recurrent nodal involvement. In a randomised, controlled trial in 280 patients, 143 patients received INTRON A therapy at 20 million IU/m² intravenously five times per week for 4 weeks (induction phase) followed by 10 million IU/m² subcutaneously three times per week for 48 weeks (maintenance phase). INTRON A therapy was begun ≤56 days after surgical resection. The remaining 137 patients were observed.

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

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

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

Pharmacokinetics

The pharmacokinetics of INTRON A after single doses administered subcutaneously, intramuscularly and as a 30-minute intravenous infusion has been studied in healthy male volunteers. In one study involving 12 subjects, single 5 million IU/m² doses were administered by the three routes. Serum concentrations of interferon alfa-2b were determined by a radio-immunoassay (RIA) with a detection limit of 10 IU/mL. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. Maximum serum levels (18-116 IU/mL) occurred at 3 to 12 hours post-injection. The elimination half-lives of interferon following both injections were 2 to 3 hours. Serum levels were below the detection limit 16 hours post-injection.

After intravenous administration, serum interferon levels peaked (135-273 IU/mL) at the end of the infusion, then declined at a slightly more rapid rate than after subcutaneous or

intramuscular administration, becoming undetectable 4 hours after the infusion. The elimination half-life was approximately 2 hours.

In another study also involving 12 subjects, single 10 million IU doses were administered by the same three routes of administration. Mean serum interferon concentrations were again comparable following intramuscular and subcutaneous injections, with maximum serum levels (150-180 IU/mL) occurring at 6 to 8 hours post-injection. The elimination half-lives following both injections were 6 to 7 hours. Serum levels were below the detection limit of 25 IU/mL 24 hours post-injection.

As with the other study, after intravenous administration, serum interferon levels peaked (546 IU/mL) at the end of the infusion, then declined rapidly with time, becoming undetectable 4 hours after the infusion.

Urine levels of interferon were below the detection limit following each of the three routes of administration in both studies.

Interferon neutralising factor assays were performed on serum samples of patients who received INTRON A in Schering Plough monitored clinical trials. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9% and in hepatitis patients, 6.9%. The detected titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon.

INDICATIONS

INTRON A is used in the treatment of:

- Hairy cell leukaemia in splenectomised or non-splenectomised patients
- Kaposi's sarcoma in patients with acquired immune deficiency syndrome (AIDS)
- Chronic myelogenous leukaemia
- Multiple myeloma
- Follicular non-Hodgkin's lymphoma
- Malignant melanoma
- Chronic hepatitis B
- Chronic hepatitis C

CONTRAINDICATIONS

A history of hypersensitivity to recombinant interferon alfa-2b or any other components of INTRON A contraindicates its use. Hypersensitivity to other forms of interferon alfa should lead to extreme caution with the use of INTRON A.

Patients with decompensated liver disease, autoimmune hepatitis or a history of autoimmune liver disease, and patients who are immunosuppressed transplant recipients should not be treated with INTRON A for chronic hepatitis. There are reports of worsening liver disease, including jaundice, hepatic encephalopathy, hepatic failure and death following INTRON A therapy in such patients.

INTRON A is not intended for use in premature infants or neonates. However, if such use is contemplated by a physician, the occurrence of a potentially fatal gasping syndrome in neonates due to the use of benzyl alcohol containing products should be borne in mind. Bacteriostatic Water for Injection contains benzyl alcohol, and it should not be used as a diluent in the neonate.

PRECAUTIONS

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

Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases, termination of INTRON A therapy.

INTRON A should be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g. chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution should be observed also in patients with coagulation disorder (e.g. thrombophlebitis, pulmonary embolism) or severe myelosuppression.

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, diarrhoea, 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.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever should not be overlooked.

In patients with liver disease, exacerbation of hepatic enzyme abnormalities may occur. Monitoring of liver function tests is advised. Hepatotoxicity resulting in fatality has been observed rarely. Therefore, any patient developing liver function abnormalities during treatment with INTRON A should be monitored closely and treatment discontinued if signs and symptoms progress.

In patients considered for treatment of hepatitis, a liver biopsy should be performed to document diagnosis and extent of disease. Patients with causes of chronic hepatitis other than chronic hepatitis B or chronic hepatitis C, including autoimmune hepatitis, should be excluded. Prior to initiation of INTRON A therapy, the physician should establish that the patient has compensated liver disease. INTRON A should not be used in patients with decompensated liver disease.

Patients with chronic hepatitis B with evidence of decreasing hepatic synthetic function (e.g. decreasing albumin 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 during INTRON A treatment [see Laboratory Tests under Precautions]. In considering these patients for INTRON A therapy, the potential risks must be evaluated against the potential benefits of treatment.

Results of two studies indicate that the efficacy of interferon therapy remains uncertain in chronic active hepatitis B in children or in adults where the presumed route of transmission is vertical.

Infrequently, patients treated for chronic hepatitis C with INTRON A developed thyroid abnormalities (hypothyroid or hyperthyroid). In clinical trials <1% (4/426) developed thyroid abnormalities. The abnormalities were controlled by conventional therapy for thyroid dysfunction. The mechanism by which INTRON A may alter thyroid status is unknown. Prior to initiation of INTRON A therapy for the treatment of chronic hepatitis C, serum thyroid-stimulating hormone (TSH) levels should be evaluated. Any thyroid abnormality detected at that time should be treated with conventional therapy. INTRON A treatment may be initiated if TSH levels can be maintained in the normal range by medication.

INTRON A should not be administered to patients with chronic hepatitis with decompensated hepatic disease, to patients with autoimmune hepatitis or history of autoimmune disease or to

immunosuppressed transplant recipients because INTRON A therapy may lead to worsening of liver disease in these patients.

If, during the course of INTRON A therapy, a patient develops symptoms consistent with possible thyroid dysfunction, TSH levels should be evaluated. In the presence of thyroid dysfunction, INTRON A treatment may be continued only if TSH levels can be maintained in the normal range by medication. Discontinuation of INTRON A therapy has not reversed thyroid dysfunction occurring during treatment.

Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

Hypotension may occur during INTRON A administration or up to two days post-therapy and may require supportive therapy.

Adequate hydration should be maintained in patients undergoing INTRON A therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement to maintain intravascular volume may be necessary.

Preliminary data indicates that interferon alfa therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection also has been reported but causal association with interferon alpha therapy has not been established.

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 sarcoma who require INTRON A therapy, should be closely monitored. Cardiomyopathy, sometimes reversible upon discontinuation of interferon alfa, has been reported rarely in AIDS-related Kaposi's sarcoma patients treated with INTRON A. 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) usually respond to conventional therapy but may require discontinuation of INTRON A therapy.

Cardiomyopathy was reported in approximately 2% of the AIDS-related Kaposi's sarcoma patients treated with INTRON A. Cardiomyopathy has also been reported in AIDS patients not receiving INTRON A therapy. Baseline chest X-rays are suggested and should be repeated if clinically indicated.

Pulmonary infiltrates, pneumonitis and pneumonia, including fatality, have been observed rarely in patients treated with interferon alfa including those treated with INTRON A. The aetiology has not been defined. Any patient developing fever, cough, dyspnoea or other respiratory symptoms should have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient should be monitored closely, and if appropriate, interferon alfa treatment should be discontinued. While this has been reported more often in patients with chronic hepatitis C treated with interferon alfa, it has also been reported in patients with oncological diseases treated with interferon alfa. Prompt discontinuation of interferon alfa administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events. Moreover, these symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon-alpha.

Patients with a pre-existing psychiatric condition or a history of severe psychiatric disorder should not be treated with INTRON A.

If severe central nervous system (CNS) effects, particularly depression, are observed, INTRON A therapy should be discontinued. Severe central nervous system (CNS) effects particularly depression, homicidal ideation, suicidal ideation, suicide or attempted suicide have been observed in some patients during INTRON A therapy. Other CNS effects including aggressive behaviour, sometimes directed towards others, psychosis including hallucinations, confusion and alterations of mental status have been observed. 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, including cases of

encephalopathy, have been observed in some patients (especially at high doses and in the elderly). While these effects are generally reversible, 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 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. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician. If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behaviour towards others is identified, it is recommended that treatment with INTRON A be discontinued, and the patient followed with psychiatric intervention as appropriate.

Narcotics, hypnotics or sedatives should be administered with caution if administered concomitantly with INTRON A.

Because of reports of exacerbating pre-existing psoriatic disease and sarcoidosis, INTRON A should be used in patients with psoriasis or sarcoidosis only if the potential benefit justifies the potential risk.

The use of INTRON A has been associated with the exacerbation of autoimmune disease, therefore, when administering INTRON A to patients with a history of, or predisposition to autoimmune disease, this should be considered.

In patients with AIDS-related Kaposi's Sarcoma, INTRON A therapy should not be used in the presence of rapidly progressive visceral disease. Patients receiving concomitant zidovudine have had a higher incidence of neutropenia than that expected with zidovudine alone. The effects of INTRON A when combined with other drugs used in the treatment of AIDS-related disease are unknown.

Ophthalmologic disorders, including retinal haemorrhage, cotton-wool spots, optic neuritis, papilledema and retinal artery or vein obstruction have been reported in rare instances after treatment with interferon alfa, including INTRON A (see ADVERSE REACTIONS). All patients should have a baseline examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual fields must have a prompt and complete eye examination. Because the retinal events may occur in conjunction with other disease states, periodic visual examinations during Intron A therapy are recommended prior to treatment with interferon 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.

Effect on Fertility

Interferon may impair fertility. In studies on interferon use in non-human primates, abnormalities of the menstrual cycle have been observed. Decreased serum oestradiol and progesterone concentrations have been reported in women treated with human leucocyte interferon. Therefore, fertile women should not receive INTRON A unless they are using effective contraception during the treatment period. INTRON A should be used with caution in fertile men.

Use in Pregnancy (Category B3)

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

Interferon has been shown to have abortifacient effects in rhesus monkeys (*Macaca mulatta*). Abortion was observed in all dose groups (7.5, 15 and 30 million IU/day IM from Day 20 to Day 80 of gestation), and was statistically significant versus control in the mid- and high-dose groups.

There are no adequate and well controlled studies in pregnant women. INTRON A should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use during Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions from INTRON A in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children

Experience in patients below 18 years of age has been limited and in such cases the expected benefits should be carefully weighed against potential hazards. Results of two studies indicate that the efficacy of interferon therapy remains uncertain in children with chronic active hepatitis B where the presumed route of transmission is vertical.

Concomitant Therapy and Drug Interactions

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

A synergistic adverse effect on the white blood cell count may occur when INTRON A is administered concomitantly with zidovudine. Patients receiving the two agents concomitantly have had a dose-dependent higher incidence of neutropenia than expected when zidovudine is administered alone.

[See Concomitant Therapy under Dosage and Administration]

Laboratory Tests

The following laboratory tests should be conducted prior to and periodically during INTRON A treatment for all patients:-

- Standard haematological tests including complete blood counts (CBC), differential white blood cell counts and platelet;
- Blood chemistry including electrolytes, liver function tests, serum creatinine, serum protein and TSH

The haematological parameters of the patients should be followed closely as part of the treatment because a certain degree of myelodepression has been reported in some patients treated with INTRON A.

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

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

Multiple myeloma: Since multiple myeloma may impair renal function, patients should have renal tests performed periodically.

Malignant melanoma: Liver function and white blood cell (WBC) count and differential should be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Chronic hepatitis B: CBC and platelet counts should be evaluated prior to initiation of INTRON A therapy in order to establish baselines for monitoring potential toxicity. These tests should be

repeated at treatment Weeks 1, 2, 4, 8, 12 and 16. Liver function tests, including serum ALT, albumin and bilirubin, should be evaluated at treatment Weeks 1, 2, 4, 8, 12 and 16. HBeAg, HBsAg and ALT should be evaluated at the end of therapy as well as 3 and 6 months post therapy, since patients may become virological responders during the 6 month period following the end of treatment.

A transient increase in ALT ≥ 2 times baseline value (flare) can occur during INTRON A therapy for chronic 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 non-responders (27%, 13/48). Elevations in bilirubin ≥ 3 mg/dL (51.3 μ mol/L) occurred infrequently (2%, 2/86) during therapy.

When ALT flare occurs, in general, INTRON A therapy should be continued unless signs and symptoms of liver failure are observed. During ALT flare, clinical symptomatology and liver function tests including ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin should be monitored at approximately 2-week intervals.

Chronic hepatitis C: Prior to initiation of INTRON A therapy, CBC and platelet counts should be evaluated in order to establish baselines for monitoring potential toxicity. These tests should be repeated at Weeks 1 and 2 following initiation of INTRON A therapy, and monthly thereafter. Serum ALT should be evaluated after 2, 16 and 24 weeks of therapy to assess response to treatment.

ADVERSE REACTIONS

Adverse reactions of INTRON A are dose-related. Haematological, hepatic, cardiovascular and neurological toxicities are more common with higher doses.

The most frequently reported adverse reactions were flu-like symptoms, primarily fever, fatigue, headache, myalgia, rigors/chills and malaise which occurred in almost all patients treated. These effects were reversible within 72 hours of interruption or cessation of treatment and were dose-related.

Other less frequent adverse reactions reported with INTRON A therapy include:

Cardiovascular System

Less common: Hypotension

Rarely reported: Tachycardia, hypertension, peripheral ischaemia, chest pain, cardiomyopathy (see below)

Very rarely reported: Palpitations, postural hypotension, bradycardia, cardiac failure, atrial fibrillation, arrhythmia, extrasystole, angina pectoris, thrombophlebitis, cardiac ischaemia, myocardial infarction, cerebrovascular haemorrhage, cerebrovascular ischaemia.

Cardiovascular adverse reactions, particularly arrhythmia appeared to be correlated mostly with pre-existing CVS disease and prior cardiotoxic therapy (see Precautions). Cardiomyopathy, that may be reversible upon discontinuation of interferon alfa has been reported rarely in patients without prior evidence of cardiac disease.

Central and Peripheral Nervous System (including psychiatric adverse reactions)

Less common: Dizziness, somnolence, insomnia, confusion, impaired concentration, depression, irritability, suicidal ideation, suicide attempts, suicide.

Rarely reported: Paraesthesia, impaired consciousness (including cases of encephalopathy, see PRECAUTIONS), migraine, hypo-aesthesia, nervousness, anxiety, seizures, agitation, emotional lability, flushing, peripheral neuropathy, neuropathy, polyneuropathy, psychosis including hallucinations, aggressive behaviour towards others, vertigo

Very rarely reported: Amnesia, stupor, convulsions, hypertonia, hyperaesthesia, hot flushes, encephalopathy, tremor, coma, extrapyramidal disorder, paresis, speech disorder, syncope,

tinnitus, abnormal coordination, ataxia, aphasia, CNS dysfunction, abnormal gait, hyperkinesia, dystonia, paralysis, impotence, personality disorder, abnormal thinking, suicide attempt, paroniria, apathy, aggravated depression, neurosis, feeling of ebriety, dementia

Endocrine System

Rarely reported: Hyperthyroidism, hypothyroidism, diabetes mellitus/hyperglycaemia

Very rarely reported: Gynaecomastia, virilism, aggravation of diabetes, pancreatitis

Gastrointestinal System

Common: Nausea

Less common: Vomiting, diarrhoea

Rarely reported: Abdominal pain, dyspepsia, loose stool, taste perversion, gingival bleeding, stomatitis, constipation, right upper quadrant (RUQ) pain, glossitis.

Very rarely reported: Eructation, tenesmus, ileus, colitis, thirst, melena, increased saliva, esophagitis, rectal bleeding after stool, dysphagia, gastrointestinal haemorrhage, gastric ulcer, gingivitis, gum hyperplasia, rectal haemorrhage, oral leucoplakia, gastrointestinal mucosal discolouration, abdominal distention, flatulence, tongue discolouration, taste loss.

Haematological System [See Laboratory Values under Adverse Reactions]

Very rarely reported: Haemolytic anaemia, increased gamma globulins, coagulation disorder

Very rarely, alfa interferons, including INTRON A used alone or in combination with Rebetol (Rebetron Combination Therapy) may be associated with aplastic anaemia or pure red cell aplasia.

Liver and Biliary System

Rarely reported: Hepatotoxicity including fatality

Very rarely reported: Abnormal hepatic function tests, bilirubinaemia, jaundice, hepatosplenomegaly, splenomegaly, hepatic encephalopathy

Musculo-Skeletal System

Common: Arthralgia, back pain

Less Common: Musculoskeletal pain

Rarely reported: Rhabdomyolysis (sometimes serious) myositis

Very rarely reported: Bone pain, muscle weakness, arthritis, arthrosis, myopathy

Reproductive System

Rarely reported: Menstrual disorders eg menorrhagia, amenorrhoea

Very rarely reported: Leucorrhoea, uterine bleeding, vaginal haemorrhage,

Resistant Mechanism Disorders

Rarely reported: Resistance mechanism disorders (eg. altered resistance to infection; these effects rarely have been life-threatening or fatal), viral infections, conjunctivitis.

Very rarely reported: Sty, fungal infections, monilliasis, sepsis

Respiratory System

Rarely reported: Coughing, pharyngitis, dyspnoea, pulmonary infiltrates, pneumonitis, pneumonia, nasal congestion, sinusitis, rhinitis, respiratory disorder.

Very rarely reported: Hypoxia, stridor, bronchospasm, cyanosis, wheezing, pleural pain, sneezing, nonproductive coughing, pulmonary embolism, pulmonary oedema, laryngitis

Skin and Appendages

Less common: Alopecia, increased sweating

Rarely reported: Rash (eg. erythematous and maculopapular), injection site disorders pruritis, dermatitis, dry skin, erythema.

Very rarely reported: Urticaria, acne, nail disorders, purpura, peripheral ischaemia, furunculosis, non-herpetic cold sores, epidermal necrolysis, lacrimal gland disorder, photosensitivity, skin discolouration, chloasma, abnormal hair texture, increased hair growth, skin depigmentation, dermatitis lichenoides, melanosis, vitiligo, injection site necrosis, toxic epidermal necrolysis, erythema multiforme, Steven Johnson syndrome.

Urinary System

Rarely reported: Renal insufficiency, renal failure, hyperuricaemia.

Very rarely reported: Micturition disorder, nocturia, polyuria, haematuria, micturition frequency, cystitis, oliguria, nephrosis, urinary incontinence, nephrotic syndrome.

Visual and Auditory Disorders

Rarely reported: Eye pain, hearing disorder, abnormal/blurred vision, hearing loss, retinal haemorrhage, retinopathies (including macular oedema), cotton wool spots, and renal artery or vein obstruction, loss of visual acuity or visual field, optic neuritis and papilloedema, lacrimal gland disorder.

Very rarely reported: Conjunctivitis, photophobia, blurred vision, diplopia, dry eyes, oculomotor nerve paralysis, retinal disorder, night blindness, earache, deafness, hyperacusis

General

Common: Anorexia

Less common: Asthenia, dry mouth, flu-like symptoms (unspecified), pain, taste alteration

Rarely reported: Herpes simplex, epistaxis, weight decrease, increased appetite, decreased libido, weakness, leg cramps, face oedema

Very rarely reported: Dehydration, hypercalcaemia, cachexia, peripheral oedema, lymphadenopathy, periorbital oedema, malignant hyperpyrexia, transplant rejection, acidosis, hypertriglyceridaemia, sarcoidosis or exacerbation of sarcoidosis.

A wide variety of autoimmune and immune-mediated disorders have been reported with alfa interferons including idiopathic thrombocytopenic purpura and 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, and bacterial infection (including sepsis), have been reported.

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

Laboratory Values

Clinically significant laboratory abnormalities, most frequently occurring at doses greater than 10 million IU daily, include reduction in granulocyte and white blood cell counts; decreases in haemoglobin level and platelet count; increases in alkaline phosphatase, lactate dehydrogenase (LDH), serum creatinine, serum urea nitrogen levels 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 levels have been noted as an abnormality in some non-hepatitis subjects and also in some patients with hepatitis particularly those with chronic hepatitis B coincident with clearance of viral DNAp.

DOSAGE AND ADMINISTRATION

INTRON A may be administered using either sterilised glass or plastic disposable syringes.

During the course of treatment with INTRON A for any indication, if adverse reactions develop, the dosage should be modified or therapy should be discontinued temporarily until the adverse reactions abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, the treatment with INTRON A should be discontinued.

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

Hairy Cell Leukaemia

The recommended dosage of INTRON A is 2 million IU/m² administered subcutaneously 3 times a week (every other day). Higher doses are not recommended. Normalisation of one or more haematological variables usually begins within 2 months of therapy. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require 6 months or more. Non-splenectomised patients responded similarly to splenectomised patients and showed similar demonstrable improvement in transfusion requirements. This dosage regimen should be maintained unless the disease progresses rapidly or severe intolerance is manifested.

The minimum effective dose of INTRON A has not been established.

Kaposi's Sarcoma

The recommended dosage for INTRON A Injection is 30 million IU/m² three times a week, to be administered subcutaneously.

This regimen should be maintained indefinitely unless the disease progresses rapidly or severe intolerance is manifested.

Chronic Myelogenous Leukaemia

The recommended dosage of INTRON A Injection is 4 to 5 million IU/m² administered daily subcutaneously. When the white blood count is controlled, the dosage may be administered three times a week (every other day).

The dosage may be adjusted according to patient's tolerance to the medication. This regimen should be maintained unless the disease progresses rapidly or severe intolerance is manifested.

Multiple Myeloma

INTRON A Injection should be administered subcutaneously three times a week (every other day) beginning at a dose of 2 million IU/m². Depending upon tolerance, the dosage should be progressively increased weekly to the maximum tolerated dose (5-10 million IU/m²) and

administered three times a week. Administration should be continued unless the disease progresses rapidly or severe intolerance is manifested.

Follicular Non-Hodgkin's Lymphoma

INTRON A is used adjunctively with chemotherapy in the treatment of follicular lymphomas. The recommended dosage is 5 million IU administered subcutaneously, three times a week (every other day).

Malignant Melanoma

As induction therapy, INTRON A is administered intravenously at a dose of 20 million IU/m² daily for five days a week over a four-week period (refer to "Preparation of INTRON A Powder for Injection for Intravenous Infusion" and "Preparation of INTRON A (HSA-free) Solution for Injection for Intravenous Infusion"). As maintenance treatment, the recommended dose is 10 million IU/m² administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse reactions develop during INTRON A treatment, particularly if granulocytes decrease to <500/mm³ or ALT/AST rises to >5x upper limit of normal, treatment should be temporarily discontinued until the adverse reactions 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/mm³ or ALT/AST rises to >10x upper limit of normal, INTRON A therapy should be discontinued.

There is no evidence that dose modifications beyond those described will result in maintenance of clinical benefit. For full clinical benefit, patients should be treated at the recommended doses, with dose modification for toxicity as described.

Chronic Hepatitis B

The lowest effective dose of INTRON A Injection is 3 million IU three times a week, administered subcutaneously.

Patients with low baseline HBV-DNA (i.e. <100 pcg) have the best response to INTRON A Injection therapy and most responders will show a 50% decrease in HBV-DNA within one month.

Patients at high risk (HBV-DNA >100 pcg), or patients who do not respond within one month may be treated at doses of 5 million IU three times weekly or up to 5 million IU daily.

The dosage may be adjusted according to the patient's tolerance to medication. With a response the selected regimen should be maintained up to four months, unless severe intolerance develops.

Chronic Hepatitis C

The recommended dose is 3 million IU administered subcutaneously three times a week. Most patients who respond demonstrate improvement in ALT levels within 12-16 weeks. In these patients, therapy should be continued with 3 million IU three times a week for up to 18 months. In patients who fail to respond after 12-16 weeks of treatment, use of INTRON A Injection should be discontinued.

Current clinical experience in patients who remain on INTRON A Injection 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.

Concomitant Therapy

Paracetamol has been used successfully to alleviate the symptoms of fever and headache which can occur with INTRON A Injection therapy. The recommended paracetamol dosage is

500 mg to 1 g given 30 minutes before administration of INTRON A Injection. The maximum dosage of paracetamol to be given is 1 g four times daily.

Stability of Injectable Solution

Single dose vials: After opening, use once and discard any residue.

As with all parenteral drug products, the solution should be inspected visually for particulate matter and discolouration prior to administration..

Preparation of INTRON A (HSA-free) Solution for Injection for Intravenous Infusion

For Malignant Melanoma:

The infusion should be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, the final concentration of interferon alfa-2b (HSA-free solution) in sterile normal saline (0.9%) must not be less than 0.3 million IU/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° to 25°C.

Compatibility with Other Intravenous Fluids

In addition to sterile normal saline solution, INTRON A Injection, at final concentrations of 0.5 to 1 million IU/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, Lactated Ringers Injection, Amino Acid Injections, and 5% Sodium Bicarbonate Injection.

NO OTHER DRUG CAN BE INFUSED CONCOMITANTLY WITH INTRON A SOLUTION FOR INJECTION.

OVERDOSAGE

Most adverse reactions to recombinant interferon alfa-2b listed are dose-related. There is no specific antidote in the event of overdose. Symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

MEDICINE CLASSIFICATION

Prescription Only Medicine

PACKAGE QUANTITIES

INTRON A Injectable Solution:

HSA-free: 10 million IU/1 mL, 18 million IU/3 mL; 25 million IU/2.5 mL in packs of 1 vial.

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