The content of this leaflet was updated according to the guidelines of the Ministry of Health in October 2017.

1. NAME OF THE MEDICINAL PRODUCT

Intron A multidose pen for injection 18 MIU.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pen contains 18 million IU of recombinant interferon alfa-2b produced in *E. coli* by recombinant DNA technology, in 1.2 ml solution.

One ml contains 15 million IU of interferon alfa-2b.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intron A is indicated in adult patients for the treatment of:

Malignant melanoma
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.

Chronic myelogenous leukaemia
Treatment of adult patients with Chronic Myelogenous Leukaemia.

Hairy cell leukaemia
Treatment of patients 18 years of age or older with hairy cell leukaemia.

AIDS-related Kaposi's sarcoma
Treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. Studies have demonstrated a greater likelihood of response to INTRON A therapy in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system.

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

When disease stabilization or a response to treatment occurs, treatment should continue until there is no further evidence of tumour or until discontinuation is required by evidence of a severe opportunistic infection or adverse effect (see section 4.2). For patients with progressive, asymptomatic Kaposi's Sarcoma who have a CD4 count $\geq 250/mm^3$, AIDS patients with CD4 counts $<250/mm^3$ or those with a history of opportunistic infections or constitutional symptoms, are unlikely to respond to INTRON A therapy and therefore should not be treated (see section 4.4).

Chronic hepatitis C

Treatment of chronic hepatitis C known for at least 6 months in patients 18 years of age or older with compensated liver disease who have a history of blood or blood product exposure and/or are HCV antibody positive by the ELISA method (anti-HCV) and one of two RIBA (Radioimmunoblotting) or HCV-RNA in PCR tests. Studies in these patients demonstrated that INTRON A therapy can produce clinically meaningful effects on this disease, manifested by normalization of serum alanine aminotransferase (ALT) and reduction in liver necrosis and degeneration.
A liver biopsy should be performed to establish the diagnosis of chronic hepatitis and show an inflammatory process at least in the portal tracks. Patients should be tested for the presence of antibody to HCV.

Chronic hepatitis B

Treatment of chronic hepatitis B in patients 18 years of age or older with compensated liver disease and HBV replication. Patients must be serum HBsAg positive for at least 6 months and have HBV replication (serum HbeAg positive or HBV-DNA in the serum) with elevated serum ALT.
Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA and improvement in liver histology. In patients with loss of HBsAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Prior to initiation of INTRON A therapy, it is recommended that a liver biopsy be performed to establish the presence of chronic hepatitis and show inflammatory activity at least in the portal tracks, and the extent of liver damage. The physician should establish that the patient has compensated liver disease.

The authorization to use the product for these Hepatitis B and C indications is subject to prior approval of the treatment by a committee which shall be appointed in each hospital and medical institution.

The names of the members of the committee shall be communicated to the Pharmaceutical Administration of the Ministry of Health.

In patients who fail to respond after three to four months of treatment, discontinuation of interferon alfa-2b therapy should be considered.

Treatment of metastatic or recurrent renal cell carcinoma

Non-Hodgkin's lymphoma
Adjuvant treatment of high tumour burden follicular lymphoma (stage III or IV) in combination with appropriate chemotherapy, such as a CHOP-like regimen.
High tumour burden is defined as having at least one of the following: bulky tumour mass (>7 cm), involvement of three or more nodal sites (each >3 cm), systemic symptoms (weight loss >10%, fever >38ºC for more than 8 days, or nocturnal sweats), splenomegaly beyond the umbilicus, major organ obstruction or compression syndrome, orbital or epidural involvement, serous effusion, or leukaemia.

4.2 Posology and method of administration

IMPORTANT: Intron A Interferon alfa-2b, recombinant for Injection dosing regimens are different for each of the following indications described in this section of the product information sheet.

Treatment must be initiated by a physician experienced in the management of the disease.

Multidose presentations must be for individual patient use only.

The pen is designed to deliver its contents of 18 million IU in doses ranging from 1.5 to 6 million IU.
The pen will deliver a maximum of 12 doses of 1.5 million IU over a period not to exceed 27 days.

If adverse events develop during the course of treatment with Intron A for any indication, modify the dose or discontinue therapy temporarily until the adverse events abate. If persistent or recurrent intolerance develops following adequate dose adjustment, or disease progresses, discontinue treatment with Intron A. At the discretion of the physician, the patient may self-administer the dose for maintenance dose regimens administered subcutaneously.

Chronic hepatitis B
The recommended dose is in the range 5 to 10 million IU administered subcutaneously three times a week (every other day) for a period of 4 to 6 months.

The administered dose should be reduced by 50 % in case of occurrence of haematological disorders (white blood cells < 1,500/mm^3, granulocytes < 1,000/mm^3, thrombocytes < 100,000/mm^3). Treatment should be discontinued in case of severe leukopaenia (< 1,200/mm^3), severe neutropaenia (< 750/mm^3) or severe thrombocytopaenia (< 70,000/mm^3).

For all patients, if no improvement on serum HBV-DNA is observed after 3 to 4 months of treatment (at the maximum tolerated dose), discontinue Intron A therapy.

Chronic hepatitis C
Intron A is administered subcutaneously at a dose of 3 million IU three times a week (every other day) to adult patients, whether administered as monotherapy or in combination with ribavirin.

(See ribavirin capsules SPC for dose of ribavirin capsules and dose modification guidelines for combination therapy).

Relapse patients
Intron A is given in combination with ribavirin. Based on the results of clinical trials, in which data are available for 6 months of treatment, it is recommended that patients be treated with Intron A in combination with ribavirin for 6 months.

Naïve patients
The efficacy of Intron A is enhanced when given in combination with ribavirin. Intron A should be given alone mainly in case of intolerance or contraindication to ribavirin.

- Intron A in combination with ribavirin
Based on the results of clinical trials, in which data are available for 12 months of treatment, it is recommended that patients be treated with Intron A in combination with ribavirin for at least 6 months.

Treatment should be continued for another 6-month period (i.e., a total of 12 months) in patients who exhibit negative HCV-RNA at month 6, and with viral genotype 1 (as determined in a pre-treatment sample) and high pre-treatment viral load.

Other negative prognostic factors (age > 40 years, male gender, bridging fibrosis) should be taken into account in order to extend therapy to 12 months.

During clinical trials, patients who failed to show a virologic response after 6 months of treatment (HCV-RNA below lower limit of detection) did not become sustained virologic responders (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

- Intron A alone
The optimal duration of therapy with Intron A alone is not yet fully established, but a therapy of between 12 and 18 months is advised.

It is recommended that patients be treated with Intron A alone for at least 3 to 4 months, at which point HCV-RNA status should be determined. Treatment should be continued in patients who exhibit negative HCV-RNA.

<u>Hairy cell leukaemia</u>
The recommended dose is 2 million IU/m^2 administered subcutaneously three times a week (every other day) for both splenectomised and non-splenectomised patients. For most patients with hairy cell leukaemia, normalisation of one or more haematological variables occurs within one to two months of Intron A treatment. Improvement in all three haematological variables (granulocyte count, platelet count and haemoglobin level) may require six months or more. This regimen must be maintained unless the disease progresses rapidly or severe intolerance is manifested.

<u>Chronic myelogenous leukaemia</u>
The recommended dose of Intron A is 4 to 5 million IU/m^2 administered daily subcutaneously. Some patients have been shown to benefit from Intron A 5 million IU/m^2

administered daily subcutaneously in association with cytarabine (Ara-C) 20 mg/m^2 administered daily subcutaneously for 10 days per month (up to a maximum daily dose of 40 mg). When the white blood cell count is controlled, administer the maximum tolerated dose of Intron A (4 to 5 million IU/m^2 daily) to maintain haematological remission.
Intron A treatment must be discontinued after 8 to 12 weeks of treatment if at least a partial haematological remission or a clinically meaningful cytoreduction has not been achieved.

Non-Hodgkin's lymphoma (follicular lymphoma)
Adjunctively with chemotherapy, interferon alfa-2b may be administered subcutaneously, at a dose of 5 million IU three times a week (every other day) for a duration of 18 months. CHOP-like regimens are advised, but clinical experience is available only with CHVP (combination of cyclophosphamide, doxorubicin, teniposide and prednisolone).

Malignant melanoma
As induction therapy, interferon alfa-2b is administered intravenously at a dose of 20 million IU/m^2 daily for five days a week for a four-week period; the calculated interferon alfa-2b dose is added to sodium chloride 9 mg/ml (0.9 %) solution for injection and administered as a 20-minute infusion (see section 6.6). As maintenance treatment, the recommended dose is 10 million IU/m^2 administered subcutaneously three days a week (every other day) for 48 weeks.

If severe adverse events develop during interferon alfa-2b treatment, particularly if granulocytes decrease to < 500/mm^3 or alanine aminotransferase/aspartate aminotransferase (ALT/AST) rises to > 5 x upper limit of normal, discontinue treatment temporarily until the adverse event abates.
Interferon alfa-2b treatment is to be restarted at 50 % of the previous dose. If intolerance persists after dose adjustment or if granulocytes decrease to < 250/mm^3 or ALT/AST rises to > 10 x upper limit of normal, discontinue interferon alfa-2b therapy.

Although the optimal (minimum) dose for full clinical benefit is unknown, patients must be treated at the recommended dose, with dose reduction for toxicity as described.

AIDS-related Kaposi's sarcoma
The optimal dosage is not yet known. Efficacy has been demonstrated at a daily dose of 10 million IU administered subcutaneously. The minimum effective dose is not established. The maximum tolerated daily dose of Intron A is 20 million IU.

If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy discontinued temporarily until adverse reactions abate.
When disease stabilization or treatment response occurs, treatment should continue until there is no further evidence of tumour or until discontinuation is required by evidence of a severe opportunistic infection or adverse effect. INTRON A therapy has been administered in an outpatient regimen.

Metastatic renal cell carcinoma
As monotherapy: Optimal dose and schedule have not been determined. INTRON A has been administered subcutaneously at doses ranging from 3 to 30 million IU/m^2 either three times a week, five days per week, or daily. The highest response rates were

achieved when INTRON A was administered subcutaneously at doses of 3 to 10 million IU/m^2 three times a week.
In combination with other therapeutic agents, such as interleukin-2: Optimal dose has not been determined. INTRON A has been administered subcutaneously at doses ranging from 3 to 20 million IU/m^2 in combination with interleukin-2. In the trials reporting the highest overall response rates, INTRON A was administered subcutaneously at a dose of 6 million IU/m^2 three times a week; dose was adjusted as needed during treatment.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function (see section 4.4).
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.
- Combination of Intron A with telbivudine.

Combination therapy with ribavirin
Also see ribavirin SPC if Intron A is to be administered in combination with ribavirin in patients with chronic hepatitis C.

4.4 Special warnings and precautions for use

Psychiatric and central nervous system (CNS)
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Intron A therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alfa interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal or homicidal ideation is identified, it is recommended that treatment with Intron A be discontinued, and the patient followed, with psychiatric intervention as appropriate.

Patients with existence of, or history of severe psychiatric conditions:
If treatment with interferon alfa-2b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.

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 alfa interferon. If treatment with alfa 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 interdisciplinary 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.

Hypersensitivity reactions
Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been observed rarely during Intron A therapy. If such a reaction develops, discontinue the medicine and institute appropriate medical therapy. Transient rashes do not necessitate interruption of treatment.

Adverse experiences including prolongation of coagulation markers and liver abnormalities
Moderate to severe adverse experiences may require modification of the patient's dose regimen, or in some cases, termination of Intron A therapy. Intron A increases the risk of liver decompensation and death in patients with cirrhosis.
Discontinue treatment with Intron A in patients with chronic hepatitis who develop prolongation of coagulation markers which might indicate liver decomposition.
Any patient developing liver function abnormalities during treatment with Intron A must be monitored closely and treatment discontinued if signs and symptoms progress.
Liver enzymes and hepatic function should be closely monitored in cirrhotic patients.

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

Need for adequate hydration
Adequate hydration must be maintained in patients undergoing Intron A therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Pyrexia
While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Patients with debilitating medical conditions
Intron A must 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 must be observed also in patients

with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary conditions
Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alfa treated patients, including those treated with Intron A. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alfa (see section 4.5). Any patient developing pyrexia, 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 is to be monitored closely, and, if appropriate, discontinue interferon alfa. While this has been reported more often in patients with chronic hepatitis C treated with interferon alfa, it has also been reported in patients with oncologic diseases treated with interferon alfa. Prompt discontinuation of interferon alfa administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Ocular adverse events
Ocular adverse events (see section 4.8) including retinal haemorrhages, cotton wool spots, serous retinal detachment, and retinal artery or vein obstruction have been reported in rare instances after treatment with alfa interferons. All patients should have a baseline eye examination. Any patient complaining of changes in visual acuity or visual fields, or reporting other ophthalmologic symptoms during treatment with Intron A, must have a prompt and complete eye examination. Periodic visual examinations during Intron A therapy are recommended particularly 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.

Obtundation, coma and encephalopathy
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses. 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.

Patients with pre-existing cardiac abnormalities
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, or with AIDS-related kaposi's sarcoma, who require Intron A therapy, must be closely monitored. Cardiomyopathy, sometimes reversible upon discontinuation of interferon alfa has been reported rarely in AIDS-related kaposi's sarcoma patients treated with interferon alfa-2b. It is recommended that those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer 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. There are no data in children or adolescents with a history of cardiac disease.

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

Patients with psoriasis and sarcoidosis
Due to reports of interferon alfa 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.

Kidney and liver graft rejection
Preliminary data indicates that interferon alfa therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Auto-antibodies and autoimmune disorders
The development of auto-antibodies and autoimmune disorders has been reported during treatment with alfa interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Chronic hepatitis C, Monotherapy (thyroid abnormalities) and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

<u>Concomitant chemotherapy</u>
Administration of Intron A in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. The most commonly reported potentially life-threatening or fatal adverse events include mucositis, diarrhoea, neutropaenia, 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 (see section 4.5). When Intron A is used with hydroxyurea, the frequency and severity of cutaneous vasculitis may be increased.

<u>Chronic hepatitis C</u>
Combination therapy with ribavirin
Also see ribavirin SPC if Intron A is to be administered in combination with ribavirin in patients with chronic hepatitis C.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation.
Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Monotherapy
Infrequently, adult patients treated for chronic hepatitis C with Intron A developed thyroid

abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using Intron A therapy, 2.8 % patients overall 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, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. Intron A treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of Intron A therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, Intron A treatment may be continued 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.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Intron A and ribavirin to HAART therapy (see ribavirin SPC). Patients treated with Intron A and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia.
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

HCV/HBV *Coinfection*
Cases of hepatitis B re-activation (some with severe consequences) have been reported in patients coinfected with hepatitis B and C viruses treated with interferon. The frequency of such re-activation appears to be low.
All patients should be screened for hepatitis B before starting treatment with interferon for hepatitis C; patients co-infected with hepatitis B and C must then be monitored and managed according to current clinical guidelines.

Dental and periodontal disorders
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Intron A and ribavirin 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 Intron A and ribavirin. 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.

Aids related Kaposi's sarcoma
In patients with AIDS related Kaposi's sarcoma, Intron A should not be used in the presence of rapidly progressive visceral disease. With the exception of zidovudine, there is a lack of safety data for the combination of Interferon alfa-2b with reverse transciptase inhibitors. Patients receiving concomitant zidovudine have had higher incidence of neutropenia than that expected with zidovudine alone. The effects of Interferon alfa-2b when combined with other drugs used in the treatment of AIDS-related disease are unknown.

Laboratory Tests
Standard haematological tests and blood chemistries (complete blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are to be conducted in all patients prior to and periodically during systemic treatment with Intron A.

During treatment for hepatitis B or C the recommended testing schedule is at weeks 1, 2, 4, 8, 12, 16, and every other month, thereafter, throughout treatment. If ALT flares during Intron A therapy to greater than or equal to 2 times baseline, Intron A therapy may be continued unless signs and symptoms of liver failure are observed. During ALT flare, the following liver function tests must be monitored at two-week intervals: ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin.

In patients treated for malignant melanoma, liver function and white blood cell (WBC) count and differential must be monitored weekly during the induction phase of therapy and monthly during the maintenance phase of therapy.

Effect on fertility
Interferon may impair fertility (see section 4.6 and section 5.3).

Important information about some of the ingredients of Intron A
This medicinal product contains less than 1 mmol sodium (23 mg) per 1.2 ml, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Intron A.

Interactions between Intron A and other medicinal products have not been fully evaluated. Caution must be exercised when administering Intron A in combination with other potentially myelosuppressive agents.

Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dose adjusted if necessary.

Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alfa treated patients, including those treated with Intron A. The aetiology has not been defined. These symptoms have been reported more frequently when shosaikoto, a Chinese herbal medicine, is administered concomitantly with interferon alfa (see section 4.4).

Administration of Intron A in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration) (see section 4.4).

Also see ribavirin SPC if Intron A is to be administered in combination with ribavirin in patients with chronic hepatitis C.

A clinical trial investigating the combination of telbivudine, 600 mg daily, with pegylated interferon alfa-2a, 180 micrograms once weekly by subcutaneous administration, indicates that this combination is associated with an increased risk of developing peripheral neuropathy. The mechanism behind these events is not known (see telbivudine SPC). Moreover, the safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated. Therefore, the combination of Intron A with telbivudine is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Women of childbearing potential have to use effective contraception during treatment. Decreased serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

Intron A must be used with caution in fertile men.

Combination therapy with ribavirin

Ribavirin causes serious birth defects 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. Females of childbearing potential must use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients or their female partners must use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy

There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Intron A is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Combination therapy with ribavirin

Ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding

It is not known whether the components of this medicinal product are excreted in human milk.

Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

4.7 Effects on ability to drive and use machines

Patients are to be advised that they may develop fatigue, somnolence, or confusion during treatment with Intron A, and therefore it is recommended that they avoid driving or operating machinery.

4.8 Undesirable effects

See ribavirin SPC for ribavirin-related undesirable effects if Intron A is to be administered in combination with ribavirin in patients with chronic hepatitis C.

In clinical trials conducted in a broad range of indications and at a wide range of doses (from 6 MIU/m^2/week in hairy cell leukaemia up to 100 MIU/m^2/week in melanoma), the most commonly reported undesirable effects were pyrexia, fatigue, headache and myalgia. Pyrexia and fatigue were often reversible within 72 hours of interruption or cessation of treatment.

Adults

In clinical trials conducted in the hepatitis C population, patients were treated with Intron A alone or in combination with ribavirin for one year. All patients in these trials received 3 MIU of Intron A three times a week. In **Table 1** the frequency of patients reporting (treatment related) undesirable effects is presented from clinical trials in naïve patients treated for one year. Severity was generally mild to moderate. The adverse reactions listed in **Table 1** are based on experience from clinical trials and post-marketing. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rarely (≥1/10,000 to <1/1,000); very rarely (<1/10,000); not known.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported during clinical trials or following the marketing use of Intron A alone or in combination with ribavirin

System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Pharyngitis[*], infection viral[*]
Common:	Bronchitis, sinusitis, herpes simplex (resistance), rhinitis
Uncommon:	Bacterial infection
Rarely:	Pneumonia[§], sepsis
Not known:	Hepatitis B reactivation in HCV/HBV co-infected patients
Blood and lymphatic system disorders	
Very common:	Leukopaenia
Common:	Thrombocytopaenia, lymphadenopathy, lymphopenia
Very rarely:	Aplastic anaemia
Not known:	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders[§]	
Very rarely:	Sarcoidosis, exacerbation of sarcoidosis
Not known:	Systemic lupus erythematosus, vasculitis, rheumatoid arthritis (new or aggravated), Vogt-Koyanagi-Harada syndrome, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis[§]
Endocrine disorders	
Common:	Hypothyroidism[§], hyperthyroidism[§]

Very rarely:	Diabetes, aggravated diabetes
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hypocalcaemia, dehydration, hyperuricemia, thirst
Very rarely:	Hyperglycaemia, hypertriglyceridaemia[§], increased appetite
Psychiatric disorders[§]	
Very common:	Depression, insomnia, anxiety, emotional lability[*], agitation, nervousness
Common:	Confusion, sleep disorder, libido decreased
Rarely:	Suicide ideation
Very rarely:	Suicide, suicide attempts, aggressive behaviour (sometimes directed against others), psychosis including hallucinations
Not known:	Homicidal ideation, mental status change[§], mania, bipolar disorders
Nervous system disorders[§]	
Very common:	Dizziness, headache, concentration impaired, mouth dry
Common:	Tremor, paresthesia, hypoesthesia, migraine, flushing, somnolence, taste perversion
Uncommon:	Peripheral neuropathy
Very rarely:	Cerebrovascular haemorrhage, cerebrovascular ischaemia, seizure, impaired consciousness, encephalopathy
Not known:	Mononeuropathies, coma[§]
Eye disorders	
Very common:	Vision blurred
Common:	Conjunctivitis, vision abnormal, lacrimal gland disorder, eye pain
Rarely:	Retinal haemorrhages[§], retinopathies (including macular oedema), retinal artery or vein obstruction[§], optic neuritis, papilloedema, loss of visual acuity or visual field, cotton-wool spots[§]
Not known:	Serous retinal detachment
Ear and labyrinth	
Common:	Vertigo, tinnitus
Very rarely:	Hearing loss, hearing disorder
Cardiac disorders	
Common:	Palpitation, tachycardia
Uncommon:	Pericarditis
Rarely:	Cardiomyopathy
Very rarely:	Myocardial infarction, cardiac ischaemia
Not known:	Congestive heart failure, pericardial effusion, arrhythmia
Vascular disorders	
Common:	Hypertension
Very rarely:	Peripheral ischaemia, hypotension[§]
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea[*], coughing[*]
Common:	Epistaxis, respiratory disorder, nasal congestion,

	rhinorrhea, cough nonproductive
Very rarely:	Pulmonary infiltrates[§], pneumonitis[§]
Not known:	Pulmonary fibrosis, pulmonary arterial hypertension[#]
Gastrointestinal disorders	
Very common:	Nausea/vomiting, abdominal pain, diarrhoea, stomatitis, dyspepsia
Common:	Stomatitis ulcerative, right upper quadrant pain, glossitis, gingivitis, constipation, loose stools
Very rarely:	Pancreatitis, ischaemic colitis, ulcerative colitis, gingival bleeding
Not known:	Periodontal disorder NOS, dental disorder NOS, tongue pigmentation [§]
Hepatobiliary disorders	
Common:	Hepatomegaly
Very rarely:	Hepatotoxicity, (including fatality)
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, pruritus[*], skin dry[*], rash[*], sweating increased
Common:	Psoriasis (new or aggravated)[§], rash maculopapular, rash erythematous, eczema, erythema, skin disorder
Very rarely:	Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia, arthralgia, musculoskeletal pain
Common:	Arthritis
Very rarely:	Rhabdomyolysis, myositis, leg cramps, back pain
Renal and urinary disorders	
Common:	Micturition frequency
Very rarely:	Renal failure, renal insufficiency, nephrotic syndrome
Reproductive system and breast disorders	
Common:	Amenorrhea, breast pain, dysmenorrhea, menorrhagia, menstrual disorder, vaginal disorder
General disorders and administration site conditions	
Very common:	Injection site inflammation, injection site reaction[*], fatigue, rigors, pyrexia[§], flu-like symptoms[§], asthenia, irritability, chest pain, malaise
Common:	Injection site pain
Very rarely:	Injection site necrosis, face oedema
Investigations	
Very common:	Weight decrease

*These events were only common with Intron A alone

[§]See section 4.4

[#]Class label for interferon products, see below Pulmonary arterial hypertension

These undesirable effects have also been reported with Intron A alone.

The undesirable effects seen with hepatitis C are representative of those reported when Intron A is administered in other indications, with some anticipated dose-related increases in incidence. For example, in a trial of high-dose adjuvant Intron A treatment in patients with melanoma, incidences of fatigue, pyrexia, myalgia, neutropaenia/anaemia, anorexia, nausea and vomiting, diarrhoea, chills, flu-like symptoms, depression, alopecia, altered taste, and dizziness were greater than in the hepatitis C trials. Severity also increased with high dose therapy (WHO Grade 3 and 4, in 66 % and 14 % of patients, respectively), in comparison with the mild to moderate severity usually associated with lower doses. Undesirable effects were usually managed by dose adjustment.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4).
Cardiomyopathy, that may be reversible upon discontinuation of interferon alfa, has been reported rarely in patients without prior evidence of cardiac disease (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV-infection, cirrhosis).
Events were reported at various time points typically several months after starting treatment with interferon alfa.

A wide variety of autoimmune and immune-mediated disorders have been reported with alfa interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section 4.4).

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, LDH, serum creatinine and serum urea nitrogen levels. Moderate and usually reversible pancytopenia has 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose
No case of overdose has been reported that has led to acute clinical manifestations. However, as for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: interferon alfa-2b, ATC code: L03A B05

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 harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

The activity of Intron A is expressed in terms of IU, with 1 mg of recombinant interferon alfa-2b protein corresponding to 2.6 x $l0^8$ 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 Organisation.

The interferons are a family of small protein molecules with molecular weights of approximately 15,000 to 21,000 daltons. They are produced and secreted by cells in response to viral infections or various synthetic and biological inducers. Three major classes of interferons have been identified: alfa, beta and gamma. These three main classes are themselves not homogeneous and may contain several different molecular species of interferon. More than 14 genetically distinct human alfa interferons have been identified. Intron A has been classified as recombinant interferon alfa-2b.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Human interferon receptors, as isolated from human lymphoblastoid (Daudi) cells, appear to be highly asymmetric proteins. They exhibit selectivity for human but not murine interferons, suggesting species specificity. Studies with other interferons have demonstrated species specificity. However, certain monkey species, eg, rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

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

Recombinant interferon alfa-2b has exhibited antiproliferative effects in studies employing both animal and human cell culture systems as well as human tumour xenografts in animals. It has demonstrated significant immunomodulatory activity *in vitro*.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

Chronic hepatitis B

Current clinical experience in patients who remain on interferon alfa-2b for 4 to 6 months indicates that therapy can produce clearance of serum HBV-DNA. An improvement in liver histology has been observed. In adult patients with loss of HBeAg and HBV-DNA, a significant reduction in morbidity and mortality has been observed.

Interferon alfa-2b (6 MIU/m^2 3 times a week for 6 months) has been given to children with chronic active hepatitis B. Because of a methodological flaw, efficacy could not be demonstrated. Moreover children treated with interferon alfa-2b experienced a reduced rate of growth and some cases of depression were observed.

Chronic hepatitis C

In adult patients receiving interferon in combination with ribavirin, the achieved sustained response rate is 47%. Superior efficacy has been demonstrated with the combination of pegylated interferon with ribavirin (sustained response rate of 61% achieved in a study performed in naïve patients with a ribavirin dose > 10.6 mg/kg, $p < 0.01$).

Intron A alone or in combination with ribavirin has been studied in 4 randomised Phase III clinical trials in 2,552 interferon-naïve patients with chronic hepatitis C. The trials compared the efficacy of Intron A used alone or in combination with ribavirin. Efficacy was defined as sustained virologic response, 6 months after the end of treatment. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Intron A was administered at a dose of 3 MIU 3 times a week as monotherapy or in combination with ribavirin. The majority of patients in these clinical trials were treated for one year. All patients were followed for an additional 6 months after the end of treatment for the determination of sustained virologic response. Sustained virologic response rates for treatment groups treated for one year with Intron A alone or in combination with ribavirin (from two studies) are shown in **Table 2.**

Co-administration of Intron A with ribavirin increased the efficacy of Intron A by at least two fold for the treatment of chronic heptatitis C in naïve patients. HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. The increased response rate to the combination of Intron A + ribavirin, compared with Intron A alone, is maintained across all subgroups.

The relative benefit of combination therapy with Intron A + ribavirin is particularly significant in the most difficult to treat subgroup of patients (genotype 1 and high virus load) (**Table** 2).

Response rates in these trials were increased with compliance. Regardless of genotype, patients who received Intron A in combination with ribavirin and received ≥ 80 % of their treatment had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (56 % vs. 32 % in trial C/I98-580).

Table 2 Sustained virologic response rates with Intron A + ribavirin (one year of treatment) by genotype and viral load

HCV Genotype	**I** **N=503** **C95-132/I95-143**	**I/R** **N=505** **C95-132/I95-143**	**I/R** **N=505** **C/I98-580**
All Genotypes	**16 %**	**41 %**	**47 %**
Genotype 1	9 %	29 %	33 %
Genotype 1 ≤ 2 million copies/ml	25 %	33 %	45 %
Genotype 1 > 2 million copies/ml	3 %	27 %	29 %
Genotype 2/3	31 %	65 %	79 %

I Intron A (3 MIU 3 times a week)
I/R Intron A (3 MIU 3 times a week) + ribavirin (1,000/1,200 mg/day)

HCV/HIV Co-infected patients
Two trials have been conducted in patients co-infected with HIV and HCV. Overall, in both studies, patients who received Intron A plus ribavirin, were less likely to respond than patients who received pegylated interferon alfa-2b with ribavirin. The response to treatment in both of these trials is presented in **Table 3.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either pegylated interferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800 mg/day) or Intron A (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV.
Patients were randomized to receive either pegylated interferon alfa-2b (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or Intron A (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

Table 3	Sustained virological response based on genotype after Intron A in combination with ribavirin versus pegylated interferon alfa-2b in combination with ribavirin in HCV/HIV co-infected patients					
	Study 1[1]			**Study 2**[2]		
	pegylated interferon alfa-2b (1.5 µg/kg/ week) + ribavirin (800 mg)	Intron A (3 MIU TIW) + ribavirin (800 mg)	p value[a]	pegylated interferon alfa-2b (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d]	Intron A (3 MIU TIW) + ribavirin (800-1,200 mg)[d]	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week pegylated interferon alfa-2b and subjects ≥ 75 kg received 150 µg/week pegylated interferon alfa-2b.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Relapse patients
A total of 345 interferon alfa relapse patients were treated in two clinical trials with Intron A monotherapy or in combination with ribavirin. In these patients, the addition of ribavirin to Intron A increased by as much as 10-fold the efficacy of Intron A used alone in the treatment of chronic hepatitis C (48.6 % vs. 4.7 %). This enhancement in efficacy included loss of serum HCV (< 100 copies/ml by PCR), improvement in hepatic inflammation, and normalisation of ALT, and was sustained when measured 6 months after the end of treatment.

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non-pegylated interferon alfa-2b or non-pegylated interferon alfa-2b/ribavirin study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders' out of 492 relapsed during this study. The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97 % with a 95 % Confidence Interval of [95 %, 99 %].
SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

5.2 Pharmacokinetic properties

The pharmacokinetics of Intron A were studied in healthy volunteers following single 5 million IU/m^2 and 10 million IU doses administered subcutaneously, at 5 million IU/m^2 administered intramuscularly and as a 30-minute intravenous infusion. The mean serum interferon concentrations following subcutaneous and intramuscular injections were comparable. C_{max} occurred three to 12 hours after the lower dose and six to eight hours after the higher dose. The elimination half-lives of interferon injections were approximately two to three hours, and six to seven hours, respectively.
Serum levels were below the detection limit 16 and 24 hours, respectively, post-injection. Both subcutaneous and intramuscular administration resulted in bioavailabilities greater than 100 %.

After intravenous 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 subcutaneous or intramuscular administration of medicinal product, becoming undetectable four hours after the infusion. The elimination half-life was approximately two hours.

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

Interferon neutralising factor assays were performed on serum samples of patients who received Intron A in Schering-Plough monitored clinical trials. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors developing in cancer patients treated systemically is 2.9% and in chronic hepatitis patients is 6.2 %.
The detectable titres are low in almost all cases and have not been regularly associated with loss of response or any other autoimmune phenomenon. In patients with hepatitis, no loss of response was observed apparently due to the low titres.

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

5.3 Preclinical safety data

Although interferon is generally recognised as being species specific, toxicity studies in animals were conducted. Injections of human recombinant interferon alfa-2b for up to three months have shown no evidence of toxicity in mice, rats, and rabbits. Daily dosing of cynomolgus monkeys with 20 x 10^6 IU/kg/day for 3 months caused no remarkable toxicity. Toxicity was demonstrated in monkeys given 100 x 10^6 IU/kg/day for 3 months.

In studies of interferon use in non-human primates, abnormalities of the menstrual cycle have been observed (see section 4.4).

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 offspring of treated rats. Interferon alfa-2b has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2. Abortion was observed in all dose groups (7.5 million, 15 million and 30 million IU/kg), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended intramuscular or subcutaneous dose of 2 million IU/m^2). High doses of other forms of interferons alfa and beta are known to produce dose-related anovulatory and abortifacient effects in rhesus monkeys.

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

Intron A plus ribavirin
No studies have been conducted in juvenile animals to examine the effects of treatment with interferon alfa-2b on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see Rebetol SPC if Intron A is to be administered in combination with ribavirin).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate dibasic anhydrous
Sodium phosphate monobasic monohydrate
Edetate disodium
Sodium chloride
M-cresol
Polysorbate 80
Water for injections q.s.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products

6.3 Shelf life
15 months.
Chemical and physical in-use stability has been demonstrated for 27 days at 2ºC – 8ºC. From a microbiological point of view, once opened, the product may be stored for a maximum of 27 days at 2ºC – 8ºC. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
Store in a refrigerator (2°C – 8°C).
Do not freeze.
For storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container
1.2 ml of solution (corresponding to 18 MIU) in a pen made of a cartridge (type I glass) sealed at one end with a cap (aluminium) containing a liner (bromobutyl rubber) and at the other end by a plunger (bromobutyl rubber).
The pack size also contains 6 injection needles and 6 cleansing swabs.
Pack size of 1.

6.6 Special precautions for disposal and other handling
Not all dose forms and strengths are appropriate for some indications. Please make sure to select an appropriate dose form and strength.

Intron A, solution for injection in multidose pen is injected subcutaneously after attaching an injection needle and dialing the prescribed dose.

Remove the pen from the refrigerator approximately 30 minutes before administration to allow the injectable solution to reach room temperature (not more than 25°C).

Detailed instructions for the use of the product are provided with the package leaflet (refer to “How to self inject Intron A”).

Each pen is intended for a maximum 27 days use period and must then be discarded. A new injection needle must be used for each dose. After each use, the injection needle must be discarded safely and the pen must be returned immediately to the refrigerator. A maximum of 48 hours (two days) of exposure to 25°C is permitted over the 27 days use period to cover accidental delays in returning the pen to the refrigerator.
Sufficient needles and swabs are provided to use the Intron A pen for administering the smallest measurable doses. Instruct the patient that any extra needles and swabs that remain after the final dose has been taken from the pen must be discarded appropriately and safely.

As with all parenteral medicinal products, prior to administration inspect Intron A, solution for injection, visually for particulate matter and discolouration. The solution should be clear and colourless.

7. LICENSE HOLDER

Merck Sharp & Dohme (Isreal-1996) Ltd., P.O.Box 7121, Petah-Tikva 49170.

8. MANUFACTURER

Merck Sharp & Dohme Corp., NJ, USA.

9. MARKETING AUTHORISATION NUMBER
117.72.29898.00

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