

## **Package leaflet: Information for the user**

### **IntronA® 10 million IU/mL solution for injection or infusion** Interferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What IntronA is and what it is used for
2. What you need to know before you use IntronA
3. How to use IntronA
4. Possible side effects
5. How to store IntronA
6. Contents of the pack and other information

#### **1. What IntronA is and what it is used for**

IntronA (interferon alfa-2b) modifies the response of the body's immune system to help fight infections and severe diseases.

IntronA is used in adult patients to treat certain disorders that affect the blood, bone marrow, lymph glands, or skin and may extend into the body. Included are hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, and malignant melanoma.

IntronA is also used in adult patients for the treatment of chronic hepatitis B or C, which are viral infections of the liver.

IntronA is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

#### **2. What you need to know before you use IntronA**

##### **Do not use IntronA**

- if you are allergic to interferon or any of the other ingredients of this medicine (listed in section 6).
- if you have severe heart disease.
- if you have poor kidney or liver function.
- if you have advanced decompensated (uncontrolled) liver disease.
- if you have hepatitis and have been treated recently with medicines that suppress the immune system (other than short-term treatment with cortisone-type medicine).
- if you have a history of seizures (convulsions).
- if you have a history of autoimmune disease, or have had an organ transplant and are taking medicine that suppresses your immune system (your immune system helps protect you from infection).
- if you have thyroid disease that is not well controlled.
- if you are being treated with telbivudine (see section "Other medicines and IntronA").

Children and adolescents:

- if you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

### **Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using IntronA

- if you are pregnant or planning to become pregnant (see section “Pregnancy and breast-feeding”).
- if you are being treated for mental illness or had treatment in the past for any other nervous or mental disorder, including depression (such as feelings of sadness, dejection) or suicidal or homicidal behaviour (see section 4 “Possible side effects”). The use of interferon alfa-2b in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section “Do not use IntronA”).
- if you have cirrhosis or other liver problems (other than hepatitis B or C).
- if you have psoriasis, it may get worse during treatment with IntronA.
- when receiving IntronA, you may temporarily have a greater risk of getting an infection. Check with your doctor if you think you are getting an infection.
- if you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- if you notice unusual bleeding or bruising check with your doctor immediately.
- if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medicine seek medical help immediately.
- if you are also being treated for HIV (see section “Other medicines and IntronA”).
- if you have a current or previous infection with the hepatitis B virus, since your doctor may want to monitor you more closely.
- if you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving IntronA and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of IntronA with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

Tell your doctor if you have ever had a heart attack or a heart problem; if you have a history of breathing irregularities or pneumonia, problems with blood clotting, liver condition, thyroid problems, diabetes, or high or low blood pressure.

Tell your doctor if you have ever been treated for depression or any other psychiatric disorder; confusion; unconsciousness; thoughts of suicide or attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs).

Be sure to tell your doctor if you are taking the Chinese herbal medicine shosaikoto.

### **Other medicines and IntronA**

IntronA will add to the effects of substances that slow down your nervous system, possibly causing drowsiness. Therefore, check with your doctor or pharmacist about drinking alcoholic beverages, or taking sleeping pills, sedatives or strong pain medicines.

Tell your doctor if you are taking theophylline or aminophylline for asthma, and about all other medicines you are taking, or have taken recently, even those not prescribed, as the dose of some medicines may have to be adjusted while you are treated with IntronA.

Patients who also have HIV infection: Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of IntronA and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be

sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with IntronA and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells).

If you take telbivudine with a pegylated interferon alfa-2a or any type of injectable interferon product, your risk of developing peripheral neuropathy (numbness, tingling and/or burning sensations in the arms and/or legs) is higher. These events may also be more severe. Therefore, the combination of IntronA with telbivudine is contraindicated.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

### **IntronA with food and drink and alcohol**

While being treated with IntronA, your doctor may want you to drink extra fluids to help prevent low blood pressure.

### **Pregnancy, breast-feeding and fertility**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known.

If you are prescribed IntronA in combination with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:

- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You must use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.

- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you or your partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking IntronA. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicinal products.

### **Driving and using machines**

Do not drive or use machines if you become drowsy, tired, or confused from using this medicine.

**IntronA** contains less than 1 mmol sodium (23 mg) per 1 mL, i.e., essentially "sodium-free".

## **3. How to use IntronA**

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor has prescribed IntronA specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined the exact dosage for administration of IntronA according to your individual needs. The dosage will vary according to the disease being treated.

If you are injecting IntronA yourself, please be sure that the dose that has been prescribed for you is clearly provided with the package of medicine you receive. Dosages that are to be administered 3 times a week are best given every other day.

The usual starting dose for each condition follows; however, individual doses may vary, and the doctor may change your dose based on your specific needs:

Chronic hepatitis B: 5 to 10 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic hepatitis C: *Adults* - 3 million IU 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin or alone. *Children 3 years of age and older and adolescents* - 3 million IU/m<sup>2</sup> 3 times a week (every other day) injected subcutaneously (under the skin) in combination with ribavirin (Please also see ribavirin package leaflet).

Hairy Cell Leukaemia: 2 million IU/m<sup>2</sup>, 3 times a week (every other day) injected subcutaneously (under the skin).

Chronic Myelogenous Leukaemia: 4-5 million IU/m<sup>2</sup> daily injected subcutaneously (under the skin).

Multiple myeloma: 3 million IU/m<sup>2</sup>, 3 times a week (every other day) injected subcutaneously (under the skin).

Follicular lymphoma: Adjunctively with chemotherapy, 5 million IU 3 times a week (every other day) injected subcutaneously (under the skin).

Carcinoid tumour: 5 million IU, 3 times a week (every other day) injected subcutaneously (under the skin).

Malignant melanoma, induction therapy: 20 million IU/m<sup>2</sup>, intravenously, given daily for 5 days a week for a 4 week period. Maintenance treatment: 10 million IU/m<sup>2</sup>, 3 times a week (every other day) injected subcutaneously (under the skin).

Your doctor may prescribe a different dose of IntronA alone or in combination with other medicines (e.g., cytarabine, ribavirin). If you are prescribed IntronA in combination with another medicine, please refer also to the Package Leaflet of the medicine to be used in combination. Your doctor will determine the exact dosage schedule and regimen according to your needs. If you have the impression that the effect of IntronA is too strong or too weak, talk to your doctor or pharmacist.

#### Subcutaneous use:

IntronA is usually intended for subcutaneous use. This means that IntronA is injected with a short needle into the fatty tissue just under the skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see section "HOW TO SELF INJECT INTRONA" at the end of the leaflet).

#### Intravenous infusion:

The infusion must be prepared immediately prior to use. Any size vial may be used to measure the required dose; however, final concentration of interferon in sodium chloride solution must be not less than 0.3 million IU/mL. The appropriate dose of IntronA is withdrawn from the vial(s), added to 50 mL of 9 mg/mL (0.9 %) sodium chloride solution for injection in a PVC bag or glass bottle for intravenous use and administered over 20 minutes.

#### **No other medicinal product can be infused concomitantly with IntronA.**

One dose of IntronA is given on each scheduled day. IntronA is given either daily (5 or 7 times a week), or three times a week, every other day, for example on Monday, Wednesday, and Friday. Interferons may cause unusual tiredness; if you are injecting this medicine yourself, or giving it to a child, use it at bedtime.

Use IntronA exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take IntronA for as long as prescribed.

**If you use more IntronA than you should**

Contact your doctor or healthcare professional as soon as possible.

**If you forget to use IntronA**

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

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**

Some people get depressed when taking IntronA alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with IntronA and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**

During the one year of treatment with IntronA in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 10-12 years after completing treatment.

If any of the following side effects happen, stop taking IntronA and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing; hives; fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to IntronA. You may need urgent medical attention or hospitalisation. These very serious side effects are very rare.

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

- chest pain or persistent and severe cough; irregular or rapid heartbeat; shortness of breath, confusion, difficulty remaining alert, numbness or tingling sensation or pain in hands or feet; seizure (convulsions); trouble sleeping, thinking or concentrating; altered mental state; suicidal thoughts, suicide attempt, changed behaviour or aggressive behaviour (sometimes directed against others), hallucinations; severe stomach pain; black or tar like stools; blood in stool or urine, severe nosebleed; waxy pallor, high sugar level in blood, fever or chills beginning after a few weeks of treatment, lower back or side pain, difficult urination, problems with your eyes or your eyesight or hearing, loss of hearing, severe or painful reddening or sores on your skin or mucous membrane.

These may signal serious side effects that may need urgent medical attention. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry iron and oxygen) counts, platelets (blood clotting cells) and other laboratory values are at

acceptable levels. Moderate and usually reversible reduction in all three blood elements-white blood cells, red blood cells and platelets, has been reported.

At the beginning of treatment with IntronA, you may experience a flu-like reaction, with fever, fatigue, headache, muscle ache, joint pain and chills/rigors. Your doctor may recommend that you take paracetamol if you develop these symptoms.

Possible side effects listed below are grouped by frequency of occurrence:

<b>Very common</b>	(affects more than 1 user in 10)
<b>Common</b>	(affects 1 to 10 users in 100)
<b>Uncommon</b>	(affects 1 to 10 users in 1,000)
<b>Rare</b>	(affects 1 to 10 users in 10,000)
<b>Very rare</b>	(affects less than 1 user in 10,000)
<b>Not known</b>	(frequency cannot be estimated from the available data)

The following side effects have been reported:

*Very commonly reported side effects:*

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

*Commonly reported side effects:*

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

*Uncommonly reported side effects:*

bacterial infection, feeling of pins and needles, and pericarditis (inflammation of the lining of the heart).

*Rarely reported side effects:*

pneumonia.

*Very rarely reported side effects:*

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

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

*Not known side effects:*

Periodontal (affecting gums) and dental disorders, change in colour of the tongue, altered mental status, loss of consciousness, acute hypersensitivity reactions including urticaria (hives), angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing), bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction) have been reported, but their frequency is unknown.

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, mania (excessive or unreasonable enthusiasm), bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement), congestive heart failure, pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself), pulmonary fibrosis (scarring of the lungs), and hepatitis B reactivation in HCV/HBV co-infected patients (recurrence of hepatitis B disease) have been reported with IntronA use.

Pulmonary arterial hypertension – a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. This may occur in particular in patients with risk factors such as HIV infection or severe liver problems (cirrhosis). The side effect may develop at various time points during treatment, typically several months after starting treatment with IntronA.

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store. . By reporting side effects, you can also help provide more information on the safety of this medicine.

## **5. How to store IntronA**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Do not freeze.

For short term travelling, the solution can be kept out of the refrigerator at or below 25°C for a period up to seven days before use. IntronA can be put back in the refrigerator at any time during this seven-day period. If the medicine is not used during the seven-day period, it should be discarded.

Do not use this medicine if you notice changes in the appearance of IntronA.

Any unused medicine must be discarded after withdrawal of the dose.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What IntronA contains**

- The active substance is recombinant interferon alfa-2b. Each vial contains 10 million IU in 1 mL of solution.
- The other ingredients are disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, edetate disodium, sodium chloride, m-cresol, polysorbate 80 and water for injections.

## **What IntronA looks like and contents of the pack**

IntronA is presented as a solution for injection or infusion.  
The clear and colourless solution is contained in a glass vial.

IntronA is available in four different pack sizes:

- Pack of 1 vial
- Pack of 1 vial, 1 injection syringe of 2 mL, 1 injection needle and 1 cleansing swab
- Pack of 6 vials, 6 injection syringes of 2 mL, 6 injection needles and 6 cleansing swabs
- Pack of 12 vials, 12 injection syringes of 2 mL, 12 injection needles and 12 cleansing swabs

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder:**

Merck Sharp & Dohme B.V.  
Waarderweg 39  
2031 BN Haarlem  
The Netherlands

### **Manufacturer:**

SP Labo N.V.  
Industriepark 30  
B-2220 Heist-op-den-Berg  
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Merck Sharp & Dohme Limited  
Tel: +44 (0) 1992 467272  
medicalinformationuk@merck.com

**This leaflet was last revised in September 2018.**

### **Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

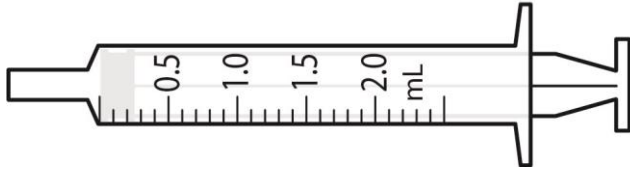
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## HOW TO SELF INJECT INTRONA

### *Syringe with an unattached needle*



The following instructions explain how to inject IntronA yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject IntronA. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

### Preparation

Collect necessary items before you begin:

- a vial of IntronA solution for injection;
- a syringe (for example 2 mL);
- a needle for the subcutaneous injection (for example 0.4 x 13 mm [27 gauge 0.5 inch]);
- a cleansing swab.

Wash your hands carefully.

### Measuring the dose of IntronA

Remove the cap from the vial. Clean the rubber stopper on the top of the vial containing the IntronA solution with a cleansing swab.

Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the needle and place it firmly onto the tip of the syringe.

Remove the needle guard without touching the needle, and fill the syringe with air by pulling the plunger to the level that represents your dose as prescribed by your doctor.

Hold the IntronA vial upright without touching the cleaned top of the vial with your hands.

Insert the needle into the vial containing the IntronA solution and inject air into the vial.

Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the IntronA solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw the correct dose as prescribed by your doctor into the syringe.

Remove the needle from the vial and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Examine the solution prior to administration: it should be clear and colourless. Do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

### Injecting the solution

Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.

Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of 45° to 90°. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.

The vial and injection materials intended for single use must be discarded. Dispose of the syringe and needle safely in a closed container.

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