PART III: CONSUMER INFORMATION

REBIF®
(Interferon beta-1a Injection)

Solution for injection in pre-filled syringes

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

ABOUT THIS MEDICATION

What the medication is used for:
REBIF is used for the treatment of relapsing forms of Multiple Sclerosis (MS) to reduce the number and the severity of clinical exacerbation and to slow the progression of disability (prolonging the time physical ability is maintained).

REBIF is also approved for use in patients who have symptoms which are likely to be a first sign of multiple sclerosis (single clinical event suggestive of multiple sclerosis). Any other reasons which could explain the symptoms have to be ruled out. Your doctor will perform a test using an imaging machine (magnetic resonance imaging [MRI]). This test has to show at least two signs of inflammation in the central nervous system suggestive of multiple sclerosis.

What it does:
Multiple sclerosis is a life-long disease the affects your nervous system (i.e., brain and spinal cord) by destroying the protective covering (myelin) that surrounds your nerve fibers. An abnormal response by the body's immune system is thought to play an important part in the process which damages the nervous system.

REBIF is a form of protein called interferon beta that occurs naturally in the body. Interferon beta has been shown to modify the immune system response, but the exact way that REBIF works in MS is unknown. REBIF will not cure MS but it has been shown to decrease the number of flare-ups and slow the occurrence of some of the physical disabilities that are common in people with MS.

When it should not be used:
REBIF should not be used if:

- You have a known hypersensitivity to any component of the formulation,
- You have severe liver disease.

What the medicinal ingredient is:
Interferon beta-1a

What the important nonmedicinal ingredients are:
Mannitol, benzyl alcohol, poloxamer-188, methionine

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
REBIF is available as a solution (liquid) in a pre-filled syringe, for subcutaneous injection.

REBIF in pre-filled syringe is available in:

- 22 mcg/0.5 mL (light green packaging, contains 3 syringes)
- 44 mcg/0.5 mL (dark green packaging, contains 3 syringes)

WARNINGS AND PRECAUTIONS

BEFORE you use REBIF talk to your doctor or pharmacist if:

- You are pregnant, think that you may be pregnant, or are planning to have a baby
- You are breastfeeding or plan to breastfeed
- You have cardiac disease, severe renal failure or severe decrease in the development of blood cells
- You have a pre-existing seizure disorder
- You have depression or suicidal thoughts
- You have liver or kidney problems
- You have problems with your thyroid gland

Women of childbearing potential:
If you are a woman of childbearing potential and are taking REBIF, you should use effective methods of contraception unless you are planning to become pregnant and have talked to your doctor about the potential risks and benefits of staying on REBIF. It is not known if interferons interfere with hormonal contraceptives.

Liver problems:
Your liver may be affected by taking REBIF and a few patients have developed severe liver injury. Your healthcare provider may ask you to have regular blood tests to make sure that your liver is working properly. If your skin or the whites of your eyes become yellow or if you are bruising easily you should call your doctor right away.

Depression:
Some patients treated with interferons, including REBIF, have become seriously depressed (feeling sad). Some patients have thought about killing themselves and a few have committed suicide. Depression (a sinking of spirits or sadness) is not uncommon in people with multiple sclerosis. However, if you are feeling noticeably sadder or helpless, or feel like hurting yourself or others, you should tell a family member or friend right away and call your doctor as soon as possible. Your doctor may ask that you stop using REBIF. You should also tell your doctor if you have ever had any mental illness, including depression, and if you take any medications for depression.

Heart problems:
Symptoms of the flu-like syndrome associated with REBIF may prove stressful to patients with cardiac conditions, such as angina, congestive heart failure or arrhythmia. If you experience symptoms

like irregular heart beat, fluid retention (swelling) in the lower parts of your body (eg, ankles, legs), or shortness of breath, call your doctor immediately.

Seizures:
Some patients have had seizures while taking interferons. It is not known whether the seizures are related to the effects of MS, to interferons, or to a combination of both. If you have a seizure while taking REBIF, you should call your doctor right away.

Thyroid problems:
Some people taking REBIF may develop changes in the function of their thyroid. Symptoms of these changes include difficulty concentrating, feeling abnormally cold or hot, gaining or losing weight without a change in your diet or the amount of exercise you are getting, feeling unusually tired or nervous and unusual very dry skin. If you experience these symptoms, you should call your doctor right away.

Kidney problems:
As with other interferon products, in rare cases, blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidney (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). This might happen several weeks to several years after starting and may cause death. Talk to your doctor if you experience the following symptoms: increased bruising, bleeding, extreme weakness, headache, dizziness or light-headedness. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

INTERACTIONS WITH THIS MEDICATION

With the exception of steroids or ACTH (anti-inflammatory medicines) that MS patients can receive during relapses, the use of REBIF was not studied together with other substances that modify the immune system response. Caution should be exercised when interferons are given in combination with other drugs which need a certain liver enzyme system (the cytochrome P450 system) for their metabolism. These drugs include some commonly used drugs against fever and pain. You should tell your doctor if you are taking any other prescription or nonprescription medicines, including vitamin and mineral supplements and herbal products.

PROPER USE OF THIS MEDICATION

Usual Dose

Patients with Relapsing-Remitting MS:
The recommended dose is 44 mcg given three times per week by subcutaneous injection. Your physician may reduce your dose to 22 mcg three times per week if you are not able to tolerate the higher dose.

Patients who have experienced a single clinical event:
The recommended dose is 44 mcg given three times per week by subcutaneous injection.

Initiating Treatment
Treatment is initiated by a gradual increase of dose in order to reduce some of the side effects.

Patients with Relapsing-Remitting MS:

- During weeks one and two, REBIF 8.8 mcg (20% of 44 mcg/0.5mL) should be injected three times per week.
- During weeks three and four, REBIF 22 mcg/0.5 mL should be injected three times per week.
- From the fifth week onwards, please see section entitled 'Usual Dose- Patients with Relapsing-Remitting MS'.

Patients who have experienced a single clinical event:

- During weeks one and two, REBIF 8.8 mcg (20% of 44 mcg/0.5mL) should be injected three times per week, as per your physician's recommendations.
- During weeks three and four, REBIF 22 mcg/0.5 mL should be injected three times per week, as per your physician's recommendations. From the fifth week onwards, please see section entitled 'Usual Dose - Patients who have experienced a single clinical event'.

Missed dose:
If you missed one dose of REBIF, continue to inject from the day of the next scheduled dose. You should not take a double dose to make up for the missed dose.

Overdosage:
If you have accidentally injected too much REBIF, do not panic. Simply contact your physician or healthcare professional for further instructions.

Administration:
When using REBIF always follow the basic principles of injection:

- Maintain sterile conditions
- Check medication
- Check expiry date
- Check dosage and instructions
- Rotate injection sites

The Six Steps of REBIF Subcutaneous Injection of Prefilled Syringes

Important: Store all injection materials and your REBIF out of the reach of children at all times.

STEP 1: Cleanse

Before you start, wash your hands well with soap and water. It is important that your hands and the items you use be as clean as possible. Needles should not touch any surface except alcohol-cleaned skin; keep them capped prior to use. Make sure you use a new syringe each time you inject to avoid contamination. Dispose of all syringes in a puncture-resistant the disposal container.

STEP 2: Assembly of injection materials

Find a clean area and lay out everything you will need (alcohol swabs, pre-filled syringe, disposal container). The injection can be given any where you feel comfortable. If you use your kitchen, ensure that all medicines and needles are kept well away from food.

STEP 3: Selecting and preparing the injection site

REBIF is injected just under the skin, in the layer of subcutaneous tissue. For your own comfort, you should avoid injecting into the same area too often. There are many possible injection sites on your body (e.g., arms, thighs, buttocks, abdomen) - refer to the diagram following these instruction or in your patient diary. It is difficult to self-inject into the back of the arm, you will likely require assistance if you choose this site. It is a good idea to plan an injection site rotation schedule and note it in a diary.

Note: Do not inject in any area in which you feel lumps, firm knots or pain. Consult your doctor or healthcare professional about any such abnormalities you find.

Use an alcohol swab to clean the skin at the selected injection site. Let the skin dry completely (15 to 20 seconds) to avoid possible burning, then discard the alcohol swab.

Optional: Autoinjector
If you have been given an autoinjector, you should follow the detailed instructions that are supplied with the unit. It is recommended that the REBIF syringe be used with the autoinjector. Many patients find that using the autoinjector, the treatment is easier to administer.

STEP 4: Preparing the REBIF injection

Remove the REBIF syringe from the blister pack by peeling back the paper covering from the arrowed end and lifting the syringe by the barrel. DO NOT ATTEMPT TO PRESS THE SYRINGE OUT THROUGH THE PAPER FROM BELOW: this may damage the needle. Keep the needle cap on.

Carefully inspect the contents of the syringe. The liquid should be clear to slightly yellow. **Do not use if the liquid is cloudy, discoloured, or contains particles.** Do not worry if there are small bubbles remaining in the solution, because injecting them subcutaneously (that is, just under the surface of the skin) will do no harm.

STEP 5: Injecting REBIF subcutaneously

Your doctor or nurse will have already advised you where to inject (e.g., abdomen, front of thigh, back of arm, buttock). Refer to the injection sites diagram (keeping a diary of injection sites as they are used is recommended). Follow the detailed instructions below each time you inject REBIF pre-filled syringes. If you have questions about injecting REBIF, contact your healthcare professional or call adveva™ at 1-888-677-3243.

Note: Your first REBIF injection should be done under the supervision of your doctor or an appropriately qualified healthcare professional.

Carefully remove the cap from the needle as follows:

- Hold the syringe vertically with the needle cap pointing upwards.
- Hold the syringe with the 4 fingers of the dominant hand (the one you write with) curled round the barrel and use the thumbnail to loosen the needle cap by lifting from under the lip of the needle cap.
- Lift the needle cap completely off the needle with a continuous vertical motion, so as not to bend the needle or touch the point.

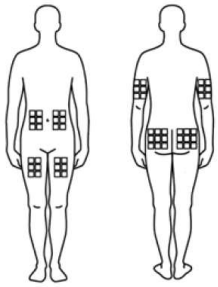
Note: If the needle is visually bent upon removal of the cap, DO NOT ATTEMPT TO STRAIGHTEN, as doing so could result in contamination and/or a painful injection. If the needle is bent, dispose of it and use a new pre-filled syringe for your injection.

- Hold the syringe like a pencil or dart.
- With your other hand, gently pinch the skin around the injection site to lift it up a bit.
- Resting your wrist on the skin near the site, use a quick, firm motion to insert the needle straight into the skin at a 90° angle.
- Inject REBIF by gently pushing the plunger all the way down. Take as much time as you need to inject all of the solution.
- Remove the needle from the skin and gently massage the injection site with a dry cotton ball or gauze.
- Discard the used syringe, needle cap and cotton ball or gauze (if used) in the disposal unit.

STEP 6: Disposal of used items

Once you have finished your injection, immediately discard the needle in the disposal container provided. When the disposal container is full, consult your clinic for the safe disposal of its contents. They should not be disposed of in household garbage.

Possible Sites for Injection of REBIF



Additional advice:
It is important that you are familiar with the correct injection technique as outlined in these instructions before beginning your treatment with REBIF.

If the injection site bleeds afterwards, firmly press a cotton ball or gauze over the injection site immediately after removing the needle. This usually stops any further bleeding.

Local skin reactions are less likely to occur if you vary the injection site. If they do occur, they usually will disappear within a few days. In the meantime, icing the area may help reduce irritation. Swelling and irritation at the injection site may also be reduced by gently massaging the area for five minutes after the injection has been given. If a generalized rash develops, you should always report it

to your doctor or nurse. Bruises may also occasionally occur at the injection site -- even when the injection has been given correctly -- but they will disappear.

Finally, remember that every treatment is individualized. REBIF has been carefully selected for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REBIF can have side effects. The most common side effects are flu-like symptoms (headache, fever, chills, muscle and joint pains, fatigue and nausea) and injection site reactions (redness, swelling, discolouration, inflammation, pain and skin breakdown). These symptoms are generally mild, are more common at the start of the treatment, and decrease with continued use. If any of these undesirable effects are severe or persist, you should contact your health care team.

In some cases, your physician may prescribe you a pain reliever (acetaminophen or ibuprofen) or may temporarily change your dose. You should not stop or alter the medication without your doctor's advice.

Should you develop multiple lesions and/or experience any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, you should consult your physician, as a decision may be required to discontinue REBIF until healing has occurred.

Other less common adverse events reported in association with interferon beta include diarrhea, loss of appetite, vomiting, inflammation of the liver, sleeping difficulty, dizziness, nervousness, itching, rash, nettle-rash, hair loss, dilatation of the blood vessels and palpitation.

Certain laboratory tests may change: the number of white blood cells or platelets may decrease and liver function tests may be disturbed. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment. Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.

Interferons may cause your thyroid gland to function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms, however your doctor may recommend testing as appropriate.

Although uncommon, there is a potential risk of liver injury. As a safety precaution, your doctors will monitor your liver function with regular laboratory testing. If you notice any symptoms such as loss of appetite with malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, please contact your doctor.

As with all interferons, female patients are recommended to use adequate contraception unless planning to become pregnant. It is not known if interferons interfere with hormonal contraceptives. Please speak to your doctor if you are pregnant or are planning on becoming pregnant.

Depression, thoughts or attempt of suicide may occur in patients with multiple sclerosis. If you have any of these feelings, please contact your physician immediately. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

There is a possibility that at the beginning of your treatment with REBIF, you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases, such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects, talk to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Flu-like symptoms (headache, fever, chills, muscle aches, fatigue, nausea)	√		
	Injection site reactions [redness, swelling, discolouration, inflammation, pain, skin breakdown, and tissue destruction (necrosis)]	√		
Uncommon	Liver injury (symptoms: loss of appetite, nausea, vomiting, fatigue, abdominal pain, dark urine)		√	
	Depression		√	

This is not a complete list of side effects. For any unexpected effects while taking REBIF, contact your doctor or pharmacist.

HOW TO STORE IT

REBIF syringes should be stored refrigerated at 2°-8°C. REBIF syringes may be stored for a limited period of time at room temperature (up to 25°C), for up to 1 month. Do not freeze.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Report Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) or by contacting the sponsor, EMD Serono, A Division of EMD Inc., Canada.

EMD Serono is a business of Merck KGaA, Darmstadt, Germany

This leaflet was prepared by EMD Serono, A Division of EMD Inc., Canada, Mississauga, Ontario, Canada L5K 2N6

If you have any questions, call adveva™ at 1-888-677-3243.

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PART III: CONSUMER INFORMATION

REBIF®
(Interferon beta-1a Injection)

Solution for injection in pre-filled cartridges

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

ABOUT THIS MEDICATION

What the medication is used for:
REBIF is used for the treatment of relapsing forms of Multiple Sclerosis (MS) to reduce the number and the severity of clinical exacerbation and to slow the progression of disability (prolonging the time physical ability is maintained).

REBIF is also approved for use in patients who have symptoms which are likely to be a first sign of multiple sclerosis (single clinical event suggestive of multiple sclerosis). Any other reasons which could explain the symptoms have to be ruled out. Your doctor will perform a test using an imaging machine (magnetic resonance imaging [MRI]). This test has to show at least two signs of inflammation in the central nervous system suggestive of multiple sclerosis.

What it does:
Multiple sclerosis is a life-long disease the affects your nervous system (i.e., brain and spinal cord) by destroying the protective covering (myelin) that surrounds your nerve fibers. An abnormal response by the body's immune system is thought to play an important part in the process which damages the nervous system.

REBIF is a form of protein called interferon beta that occurs naturally in the body. Interferon beta has been shown to modify the immune system response, but the exact way that REBIF works in MS is unknown. REBIF will not cure MS but it has been shown to decrease the number of flare-ups and slow the occurrence of some of the physical disabilities that are common in people with MS.

When it should not be used:
REBIF should not be used if:

- You have a known hypersensitivity to any component of the formulation,
- You have severe liver disease

What the medicinal ingredient is:
Interferon beta-1a

What the important nonmedicinal ingredients are:
Mannitol, benzyl alcohol, poloxamer-188, methionine

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
REBIF is available as a solution (liquid) in a pre-filled multi-dose cartridge, for subcutaneous injection.

REBIF in pre-filled cartridge is available as:

- 3 doses of 22 mcg/0.5 mL in one cartridge (66 mcg/1.5 mL). One box, light green packaging, contains 4 cartridges)
- 3 doses of 44 mcg/0.5 mL in one cartridge (132 mcg /1.5mL). One box, dark green packaging, contains 4 cartridges)

WARNINGS AND PRECAUTIONS

BEFORE you use REBIF talk to your doctor or pharmacist if:

- You are pregnant, think that you may be pregnant, or are planning to have a baby
- You are breastfeeding or plan to breastfeed
- You have cardiac disease, severe renal failure or severe decrease in the development of blood cells
- You have a pre-existing seizure disorder
- You have depression or suicidal thoughts
- You have liver or kidney problems
- You have problems with your thyroid gland

Women of childbearing potential:
If you are a woman of childbearing potential and are taking REBIF, you should use effective methods of contraception unless you are planning to become pregnant and have talked to your doctor about the potential risks and benefits of staying on REBIF. It is not known if interferons interfere with hormonal contraceptives.

Liver problems:
Your liver may be affected by taking REBIF and a few patients have developed severe liver injury. Your healthcare provider may ask you to have regular blood tests to make sure that your liver is working properly. If your skin or the whites of your eyes become yellow or if you are bruising easily you should call your doctor right away.

Depression:
Some patients treated with interferons, including REBIF, have become seriously depressed (feeling sad). Some patients have thought about killing themselves and a few have committed suicide. Depression (a sinking of spirits or sadness) is not uncommon in people with multiple sclerosis. However, if you are feeling noticeably sadder or helpless, or feel like hurting yourself or others, you should tell a family member or friend right away and call your doctor as soon as possible. Your doctor may ask that you stop using REBIF. You should also tell your doctor if you have ever had any mental illness, including depression, and if you take any medications for depression.

Heart problems:
Symptoms of the flu-like syndrome associated with REBIF may prove stressful to patients with cardiac conditions, such as angina, congestive heart failure or arrhythmia. If you experience symptoms like irregular heart beat, fluid retention (swelling) in the lower parts of your body (eg, ankles, legs), or shortness of breath, call your doctor immediately.

Seizures:
Some patients have had seizures while taking interferons. It is not known whether the seizures are related to the effects of MS, to interferons, or to a combination of both. If you have a seizure while taking REBIF, you should call your doctor right away.

Thyroid problems:
Some people taking REBIF may develop changes in the function of their thyroid. Symptoms of these changes include difficulty concentrating, feeling abnormally cold or hot, gaining or losing weight without a change in your diet or the amount of exercise you are getting, feeling unusually tired or nervous and unusual very dry skin. If you experience these symptoms, you should call your doctor right away.

Kidney problems:
As with other interferon products, in rare cases, blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidney (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). This might happen several weeks to several years after starting and may cause death. Talk to your doctor if you experience the following symptoms: increased bruising, bleeding, extreme weakness, headache, dizziness or light-headedness. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

INTERACTIONS WITH THIS MEDICATION

With the exception of steroids or ACTH (anti-inflammatory medicines) that MS patients can receive during relapses, the use of REBIF was not studied together with other substances that modify the immune system response. Caution should be exercised when interferons are given in combination with other drugs which need a certain liver enzyme system (the cytochrome P450 system) for their metabolism. These drugs include some commonly used drugs against fever and pain. You should tell your doctor if you are taking any other prescription or nonprescription medicines, including vitamin and mineral supplements and herbal products.

PROPER USE OF THIS MEDICATION

Usual Dose

Patients with Relapsing-Remitting MS:
The recommended dose is 44 mcg given three times per week by subcutaneous injection. Your physician may reduce your dose to 22 mcg three times per week if you are not able to tolerate the higher dose.

Patients who have experienced a single clinical event:
The recommended dose is 44 mcg given three times per week by subcutaneous injection.

Initiating Treatment

Treatment is initiated by a gradual increase of dose in order to reduce some of the side effects.

Patients with Relapsing-Remitting MS:
- During weeks one and two, REBIF 8.8 mcg (20% of 44 mcg/0.5mL) should be injected three times per week.
- During weeks three and four, REBIF 22 mcg/0.5 mL should be injected three times per week.
- From the fifth week onwards, please see section entitled 'Usual Dose- Patients with Relapsing-Remitting MS'.

Patients who have experienced a single clinical event:
- During weeks one and two, REBIF 8.8 mcg (20% of 44 mcg/0.5mL) should be injected three times per week, as per your physician's recommendations.
- During weeks three and four, REBIF 22 mcg/0.5 mL should be injected three times per week, as per your physician's recommendations.
- From the fifth week onwards, please see section entitled 'Usual Dose-Patients who have experienced a single clinical event'

Two alternative devices, the RebiSmart® autoinjector device and the RebiSlide® re-usable pen injector are available for administration of REBIF.

The RebiSmart autoinjector electronic device is programmed for the three times per week dosing frequency. The RebiSlide re-usable manual pen injector can be used with the three times per week and once per week dosing frequency. Please discuss with your physician which device is adequate for you.

Missed dose:
If you missed one dose of REBIF, continue to inject from the day of the next scheduled dose. You should not take a double dose to make up for the missed dose.

Overdosage:
If you have accidentally injected too much REBIF, do not panic. Simply contact your physician or healthcare professional for further instructions.

Administration:
When using REBIF always follow the basic principles of injection:
- Maintain sterile conditions
- Check medication
- Check expiry date
- Check dosage and instructions
- Rotate injection sites

Important: Store all injection materials and your REBIF out of the reach of children at all times.

STEP 1: Cleanse
Before you start, wash your hands well with soap and water. It is important that your hands and the items you use be as clean as possible. Needles should not touch any surface except alcohol-cleaned skin; keep them capped prior to use.

STEP 2: Assembly of injection materials
Find a clean area and lay out everything you will need (alcohol swabs, pre-filled cartridge, RebiSmart autoinjector device or RebiSlide re-usable pen injector, disposal container). The injection can be given anywhere you feel comfortable. If you use your kitchen, ensure that all medicines and needles are kept well away from food.

The REBIF pre-filled cartridge is ready to be used with the RebiSmart autoinjection device and the RebiSlide re-usable pen injector. For instructions on how to load the cartridge into the RebiSmart autoinjection device or the RebiSlide re-usable pen injector, please read the instructions provided with each device.

STEP 3: Selecting and preparing the injection site
REBIF is injected just under the skin, in the layer of subcutaneous tissue. For your own comfort, you should avoid injecting into the same area too often. There are many possible injection sites on your body (e.g., arms, thighs, buttocks, abdomen) - refer to the diagram following these instruction or in your patient diary. It is difficult to self-inject into the back of the arm, you will likely require assistance if you choose this site. It is a good idea to plan an injection site rotation schedule and note it in a diary.

Note: Do not inject in any area in which you feel lumps, firm knots or pain. Consult your doctor or healthcare professional about any such abnormalities you find.

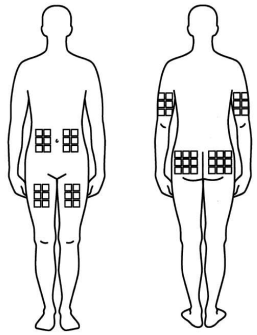
Use an alcohol swab to clean the skin at the selected injection site. Let the skin dry completely (15 to 20 seconds) to avoid possible burning, then discard the alcohol swab.

Carefully inspect the contents of the cartridge. The liquid should be clear to slightly yellow. **Do not use if the liquid is cloudy, discoloured, or contains particles.**

STEP 4: Injecting REBIF subcutaneously
Your doctor or nurse will have already advised you where to inject (e.g., abdomen, front of thigh, back of arm, buttock). Refer to the injection sites diagram (keeping a diary of injection sites as they are used is recommended). Follow the detailed instructions below each time you inject REBIF pre-filled cartridges. If you have questions about injecting REBIF, contact your healthcare professional or call adveva™ at 1-888-677-3243.

Note: Your first REBIF injection should be done under the supervision of your doctor or an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or caregiver can use REBIF cartridges with the RebiSmart autoinjector device or RebiSlide re-usable pen injector to administer the medicine at home.

Possible Sites for Injection of REBIF



Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently in order to minimize the risk of injection site necrosis.

NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

- Wash your hands thoroughly with soap and water.
- Remove the REBIF cartridge from the blister pack by peeling back the plastic covering.
- To place the cartridge in the device and perform the injection, follow the instructions in the instruction manual provided with your RebiSmart or RebiSlide. The manufacturer's instructions for using the device must be followed carefully for loading the cartridge, attaching the injection needle and administering REBIF.
- Ensure that the injection settings always correspond to the dose in the cartridge inserted in the RebiSmart

Full instructions for use are provided with the RebiSmart autoinjector device and the RebiSlide re-usable pen injector.

STEP 5: Disposal of used items
Once you have finished your injection, immediately discard the needle in the disposal container provided. When the disposal container is full, consult your clinic for the safe disposal of its contents. They should not be disposed of in household garbage.

Additional advice:
It is important that you are familiar with the correct injection technique as outlined in the instructions before beginning your treatment with REBIF.
If the injection site bleeds afterwards, firmly press a cotton ball or gauze over the injection site immediately after removing the needle. This usually stops any further bleeding.

Local skin reactions are less likely to occur if you vary the injection site. If they do occur, they usually will disappear within a few days. In the meantime, icing the area may help reduce irritation. Swelling and irritation at the injection site may also be reduced by gently massaging the area for five minutes after the injection has been given. If a generalized rash develops, you should always report it

to your doctor or nurse. Bruises may also occasionally occur at the injection site -- even when the injection has been given correctly -- but they will disappear.

Finally, remember that every treatment is individualized. REBIF has been carefully selected for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REBIF can have side effects. The most common side effects are flu-like symptoms (headache, fever, chills, muscle and joint pains, fatigue and nausea) and injection site reactions (redness, swelling, discolouration, inflammation, pain and skin breakdown). These symptoms are generally mild, are more common at the start of the treatment, and decrease with continued use. If any of these undesirable effects are severe or persist, you should contact your health care team.

In some cases, your physician may prescribe you a pain reliever (acetaminophen or ibuprofen) or may temporarily change your dose. You should not stop or alter the medication without your doctor's advice.

Should you develop multiple lesions and/or experience any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, you should consult your physician, as a decision may be required to discontinue REBIF until healing has occurred.

Other less common adverse events reported in association with interferon beta include diarrhea, loss of appetite, vomiting, inflammation of the liver, sleeping difficulty, dizziness, nervousness, itching, rash, nettle-rash, hair loss, dilatation of the blood vessels and palpitation.

Certain laboratory tests may change: the number of white blood cells or platelets may decrease and liver function tests may be disturbed. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment. Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.

Interferons may cause your thyroid gland to function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms, however your doctor may recommend testing as appropriate.

Although uncommon, there is a potential risk of liver injury. As a safety precaution, your doctors will monitor your liver function with regular laboratory testing. If you notice any symptoms such as loss of appetite with malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, please contact your doctor.

As with all interferons, female patients are recommended to use adequate contraception unless planning to become pregnant. It is not known if interferons interfere with hormonal contraceptives. Please speak to your doctor if you are pregnant or are planning on becoming pregnant.

Depression, thoughts or attempt of suicide may occur in patients with multiple sclerosis. If you have any of these feelings, please contact your physician immediately. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

There is a possibility that at the beginning of your treatment with REBIF, you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases, such symptoms are associated with fever or flu-like symptoms described above. If you noticed any of these side effects, talk to your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Flu-like symptoms (headache, fever, chills, muscle aches, fatigue, nausea)	√		
	Injection site reactions [redness, swelling, discolouration, inflammation, pain, skin breakdown, and tissue destruction (necrosis)]	√		
Uncommon	Liver injury (symptoms: loss of appetite, nausea, vomiting, fatigue, abdominal pain, dark urine)		√	
	Depression		√	

This is not a complete list of side effects. For any unexpected effects while taking REBIF, contact your doctor or pharmacist.

HOW TO STORE IT

REBIF cartridges should be stored refrigerated at 2°-8°C. REBIF cartridges may be stored for a limited period of time at room temperature (up to 25°C), for up to 1 month. Do not freeze.

Storing RebiSmart:
Refer to the storage information for REBIF cartridges as RebiSmart can be stored containing a cartridge of REBIF. Always store RebiSmart in its storage box. Do not freeze.

Storing RebiSlide:
Refer to the storage information for REBIF cartridges as RebiSlide can be stored containing a cartridge of REBIF. Always store RebiSlide in the supplied storage case. Keep away from direct sources of light and heat. Do not freeze.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Report Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) or by contacting the sponsor, EMD Serono, A Division of EMD Inc., Canada.

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If you have any questions, call adveva™ at 1-888- 677-3243.

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