Abbreviated Package Insert
See Product Monograph for complete product information at
https://www.novartis.ca/en/our-products/pharmaceuticals

PrEXTAVIA®
Interferon beta-1b

INDICATIONS AND CLINICAL USE

EXTAVIA (interferon beta-1b) is indicated for:

- the treatment of patients with a single demyelinating event accompanied by at least two clinically silent lesions typical of multiple sclerosis (MS) on magnetic resonance imaging, to delay progression to definite MS. Before initiating treatment with EXTAVIA, alternate diagnoses should first be excluded.
- the reduction of the frequency of clinical exacerbations in ambulatory patients with relapsing-remitting multiple sclerosis. Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery.
- the slowing of progression in disability and the reduction of the frequency of clinical exacerbations in patients with secondary-progressive multiple sclerosis.

The safety and efficacy of EXTAVIA in primary progressive MS have not been evaluated.

Pediatrics (<18 years of age):
Safety and efficacy in children under 18 years of age have not been established.

CONTRAINDICATIONS

- Patients with a history of hypersensitivity to natural or recombinant interferon beta, albumin human or to any other ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Patients with current severe depression and/or suicidal ideation.
- Patients with decompensated liver disease.

WARNINGS AND PRECAUTIONS

Psychiatric

Suicidal ideation is known to occur with increasing frequency in the MS population. Patients treated with EXTAVIA should be informed that depression and suicidal ideation may be a side

effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

In the RR-MS clinical trial, one suicide and four attempted suicides were observed among 372 study patients during a 3-year period. All five patients received EXTAVIA (three in the 0.05 mg [1.6 MIU] group and two in the 0.25 mg [8.0 MIU] group). There were no attempted suicides in patients on study who did not receive EXTAVIA. In the SP-MS study there were 5 suicide attempts in the placebo group and 3 in the EXTAVIA group including one patient in each group who committed suicide.

Cardiovascular

EXTAVIA (interferon beta-1b) should be used with caution in patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmias. While there is no evidence of a direct cardiotoxic potential for EXTAVIA, these patients should be monitored for worsening of their cardiac condition. This applies particularly during initiation of treatment with EXTAVIA, where flu-like symptoms, commonly associated with beta interferons, exert cardiac stress through fever, chills and tachycardia. This may aggravate cardiac symptoms in patients with pre-existing significant cardiac disease. During the postmarketing period very rare reports have been received of worsening of cardiac status in patients with pre-existing significant cardiac disease, temporally associated with the initiation of EXTAVIA therapy.

Cases of cardiomyopathy have been reported. If this occurs, and a relationship to EXTAVIA is suspected, treatment should be discontinued.

Dependence/Tolerance

No evidence or experience suggests that abuse or dependence occurs with EXTAVIA therapy; however, the risk of dependence has not been systematically evaluated.

Endocrine and Metabolism

Rare cases of thyroid dysfunction (hyper- as well as hypothyroidism) associated with the use of EXTAVIA have been reported.

Hepatic/Biliary/Pancreas

Rare post-market cases of serious hepatic injury, including autoimmune hepatitis, hepatitis and hepatic failure, have been reported with interferon beta treatment for multiple sclerosis.

It is recommended that liver function testing occur at baseline, every month for the first 6 months of treatment and at 6-month intervals thereafter. Dose reduction or discontinuation of therapy should be considered if alanine aminotransferase (ALT) levels increase 5 times above the upper limit of normal.

Interferon beta therapy should be initiated with caution in patients with a history of significant liver disease or alcohol abuse and in patients with clinical evidence of acute liver disease.

Caution must be exercised when prescribing drugs with documented hepatotoxicity to patients on interferon beta therapy for multiple sclerosis.

Cases of pancreatitis were reported with EXTAVIA use, often associated with hypertriglyceridemia.

Hypersensitivity

Serious hypersensitivity reactions (severe acute reactions such as bronchospasm, anaphylaxis and urticaria) may occur.

Pre-filled syringe, latex-sensitive individuals

The removable rubber cap of the EXTAVIA diluent (0.54% Sodium Chloride Solution) pre-filled syringe contains natural rubber latex, which may cause allergic reactions and should not be handled by latex-sensitive individuals. The safe use of EXTAVIA pre-filled syringe in latex-sensitive individuals has not been studied.

Immune

Immune system disorders

The administration of cytokines to patients with pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples in controlled clinical trials were collected every 3 months for monitoring of development of antibodies to EXTAVIA.

In the different controlled clinical trials, between 23% and 41% of the patients developed serum interferon beta-1b neutralizing activity confirmed by at least two consecutive positive titres; of these patients, between 43% and 55% converted to a stable antibody negative status (based on two consecutive negative titres) during the subsequent observational period of the respective study (see **PART II: SCIENTIFIC INFORMATION: CLINICAL TRIALS, 1. Relapsing-remitting MS** and **2. Secondary-progressive MS** subsections in Product Monograph (https://www.novartis.ca/en/our-products/pharmaceuticals)).

The development of neutralizing activity is associated with a reduction in clinical efficacy only with regard to relapse activity. Some analyses suggest that this effect might be larger in patients with higher titre levels of neutralizing activity.

In the study of patients with a single clinical event suggestive of multiple sclerosis, neutralizing activity measured every 6 months was observed at least once in 32% (88) of the patients treated

early with EXTAVIA; of these, 47% (41) returned to negative status over a 3 year period. Within this period, the development of neutralizing activity was not associated with a reduction in clinical efficacy (with regard to time to clinically definite multiple sclerosis [CDMS], and time to confirmed EDSS progression) (see **PART II: SCIENTIFIC INFORMATION: CLINICAL TRIALS, 3. Single Clinical Event Suggestive of MS** subsection in Product Monograph (https://www.novartis.ca/en/our-products/pharmaceuticals)).

New adverse events have not been associated with the development of neutralizing activity.

It has been demonstrated in vitro that EXTAVIA cross reacts with natural interferon beta. However, this has not been investigated in vivo and its clinical significance is uncertain.

There are sparse and inconclusive data on patients who have developed neutralizing activity and have completed EXTAVIA therapy.

The decision to continue or discontinue treatment should be based on clinical disease activity rather than on neutralizing activity status.

Neurologic

Cases of seizures have been reported with interferon beta therapy. EXTAVIA should be administered with caution to patients with a history of seizure, to patients receiving treatment with anti-epileptics, and in particular to patients with epilepsy who are not adequately controlled with anti-epileptics.

This product contains human albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeld-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

The effect of EXTAVIA on the ability to drive and use machinery has not been investigated. Central nervous system-related adverse events associated with the use of EXTAVIA might influence the ability to drive and use machines in susceptible patients.

Sexual Function/Reproduction

Studies in female rhesus monkeys with normal menstrual cycles, at doses up to 0.33 mg (10.7 MIU)/kg/day (equivalent to 32 times the recommended human dose based on body surface area comparison) showed no apparent adverse effects on the menstrual cycle or on associated hormonal profiles (progesterone and estradiol) when administered over 3 consecutive menstrual cycles. The extrapolability of animal doses to human doses is not known. Effects of EXTAVIA on women with normal menstrual cycles are not known.

Thrombotic Microangiopathy (TMA) and hemolytic anemia

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur after several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. If clinical features of TMA are observed, testing of blood platelet levels, serum lactate dehydrogenase (LDH), schistocytes (erythrocyte fragmentation) on a blood film with a negative Coombs test and renal function is recommended. Prompt treatment of TTP/HUS is required and immediate discontinuation of treatment with EXTAVIA is recommended.

Additionally, cases of hemolytic anemia (HA) not associated with TMA, including immune HA, have been reported with interferon beta products, including EXTAVIA. Life-threatening and fatal cases were reported.

Nephrotic Syndrome

Cases of nephrotic syndrome have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon-beta. Periodic monitoring of early signs or symptoms, e.g. edema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with EXTAVIA should be considered.

Special Populations

Pregnant Women: There are no controlled clinical studies of EXTAVIA in pregnant women. The administration of EXTAVIA during confirmed pregnancy should be avoided, unless clearly needed.

A European registry study collected data on 778 prospective pregnancies in women with MS who were treated with one of five interferon beta medications. The rates of aggregated adverse pregnancy outcomes were in line with reference ranges published in the literature.

Data from a retrospective register-based study in Sweden and Finland have likewise not indicated an increased risk of major congenital anomalies after early pregnancy exposure. However, the duration of exposure during the first trimester was uncertain since data were collected when interferon beta use was contraindicated during pregnancy, and treatment was interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester was too limited to determine whether exposure affects maternal or fetal health.

EXTAVIA was not teratogenic at doses up to 0.42 mg (13.3 MIU)/kg/day in rhesus monkeys, but demonstrated dose-related abortifacient activity when administered at doses ranging from

0.028 mg (0.89 MIU)/kg/day (2.8 times the recommended human dose based on body surface area comparison) to 0.42 mg (13.3 MIU)/kg/day (40 times the recommended human dose based on body surface area comparison). No malformations were observed in either the surviving animals or in tissues recovered post-abortion. The extrapolability of animal doses to human doses is not known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reported in 4 patients who participated in the EXTAVIA RR-MS clinical trial, whereas there was one induced abortion in each of the placebo and EXTAVIA groups in the SP-MS trial, with incidence rates not exceeding those in the general population. EXTAVIA given to rhesus monkeys on gestation days 20 to 70 did not cause teratogenic effects; however, it is not known if teratogenic effects exist in humans. There are no adequate and well-controlled studies in pregnant women.

The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot be evaluated based on the currently available data.

Women of Childbearing Age: It is not known if interferons alter the efficacy of oral contraceptives.

Nursing Women: No studies have been conducted with EXTAVIA in lactating women. Limited information available from published literature on the transfer of interferon beta into breast milk suggests that levels of interferon beta excreted in human milk are low. A risk to the nursing infant cannot be excluded.

The benefit and potential risk of breastfeeding should be considered along with the patient's medical need for interferon beta therapy.

Pediatrics (< 18 years of age): Safety and efficacy in children under 18 years of age have not been established.

Information to be Provided to the Patient

Patients should be informed of the potential risk of liver injury with interferon beta therapy, and of the requirement for frequent laboratory testing for liver function (see **Monitoring and Laboratory Tests**). Patients should be informed of the symptoms suggesting liver dysfunction, such as jaundice, malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, and pruritus, and advised to consult their physician immediately if such symptoms arise.

Patients should be instructed in injection techniques to assure the safe self-administration of EXTAVIA (see below and **PART III: CONSUMER INFORMATION**).

Instruction on self-injection technique and procedures: It is recommended that the first injection be administered by, or under the direct supervision of, a physician. Appropriate instructions for reconstitution of EXTAVIA and self-injection, using aseptic techniques, should be given to the patient. A careful review of **PART III: CONSUMER INFORMATION** is also recommended.

Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. Information on how to acquire a puncture-resistant container for disposal of used needles and syringes should be given to the patient along with instructions for safe disposal of full containers.

Overall, 80% of patients in the two controlled clinical trials reported injection site reactions at one or more times during therapy. Post-marketing experience has been consistent with this finding, with infrequent reports of injection site necrosis.

The onset of injection site necrosis usually appears early in therapy with most cases reported to have occurred in the first two to three months of therapy. The number of sites where necrosis has been observed was variable.

Rarely, the area of necrosis has extended to subcutaneous fat or fascia. Response to treatment of injection site necrosis with antibiotics and/or steroids has been variable. In some of these patients elective debridement and, less frequently, skin grafting took place to facilitate healing which could take from three to six months.

Some patients experienced healing of necrotic skin lesions while EXTAVIA therapy continued. In other cases new necrotic lesions developed even after therapy was discontinued.

The nature and severity of all reported reactions should be carefully assessed.

To minimize the risk of injection site necrosis patients should be advised to use an aseptic injection technique and rotate the injection sites with each dose. Patient understanding and use of aseptic self-injection technique and procedures should be periodically re-evaluated.

The incidence of injection site reactions may be reduced by the use of an autoinjector. In the pivotal study of patients with a single clinical event suggestive of MS an autoinjector was used by the majority of patients. Injection site reactions, as well as injection site necrosis, were observed less frequently in this study than in the other pivotal studies.

Flu-like symptoms are not uncommon following initiation of therapy with EXTAVIA. In the controlled MS clinical trials, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) were permitted for relief of fever or myalgia.

Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation.

Awareness of adverse reactions: Patients should be advised about the common adverse events associated with the use of EXTAVIA, particularly injection site reactions and the flu-like symptom complex (see **ADVERSE REACTIONS** in Product Monograph (https://www.novartis.ca/en/our-products/pharmaceuticals)).

Patients should be cautioned to report depression or suicidal ideation (see **WARNINGS AND PRECAUTIONS).**

Patients should be advised about the abortifacient potential of EXTAVIA (see **WARNINGS AND PRECAUTIONS, Special Populations – Pregnant Women**).

Monitoring and Laboratory Tests

The following laboratory tests are recommended prior to initiating EXTAVIA therapy and at periodic intervals thereafter: thyroid function test, hemoglobin, complete and differential white blood cell counts, platelet counts and blood chemistries including liver function tests. It is recommended that liver function testing occur at baseline, every month for the first 6 months of treatment and at 6-month intervals thereafter. Dose reduction or discontinuation of therapy should be considered if alanine aminotransferase (ALT) levels increase 5 times above the upper limit of normal. A pregnancy test, chest roentgenogram and ECG should also be performed prior to initiating EXTAVIA therapy. Patients with anemia, thrombocytopenia or leukopenia (alone or in any combination) may require more intensive monitoring of complete blood cell counts, with differential and platelet counts. Patients who develop neutropenia should be monitored closely for the development of fever or infection. There have been reports of thrombocytopenia, with profound decreases in platelet count.

In the controlled MS trials, patients were monitored every 3 months. The study protocol stipulated that EXTAVIA therapy be discontinued in the event the absolute neutrophil count fell below 750/mm^3. When the absolute neutrophil count had returned to a value greater than 750/mm^3, therapy could be restarted at a 50% reduced dose. No patients were withdrawn or dose-reduced for neutropenia or lymphopenia. Similarly, if AST/ALT (SGOT/SGPT) levels exceeded 10 times the upper limit of normal, or if the serum bilirubin exceeded 5 times the upper limit of normal, therapy was discontinued. In each instance, hepatic enzyme abnormalities returned to normal following discontinuation of therapy. When measurements had decreased to below these levels, therapy could be restarted at a 50% dose reduction, if clinically appropriate. Dose was reduced in two patients due to increased liver enzymes; one continued on treatment and one was ultimately withdrawn.

In the study conducted in patients with a single clinical event suggestive of MS, five EXTAVIA patients (1.7%) were withdrawn due to increased hepatic enzymes (AST/ALT), two of them after a dose reduction.

ADVERSE REACTIONS

See Product Monograph at https://www.novartis.ca/en/our-products/pharmaceuticals

DRUG INTERACTIONS

Drug-Drug Interactions

Interactions between EXTAVIA and other drugs have not been evaluated. Although studies designed to examine drug interactions have not been done, it was noted that EXTAVIA patients (n=180) have received corticosteroid or ACTH treatment of relapses for periods of up to 28 days.

Due to the lack of clinical experience in multiple sclerosis patients, the use of EXTAVIA together with immunomodulators other than corticosteroids or ACTH is not recommended.

EXTAVIA administered in three cancer patients over a dose range of 0.025 mg (0.8 MIU) to 2.2 mg (71 MIU) led to a dose-dependent inhibition of antipyrine elimination. The effect of EXTAVIA on drug metabolism in MS patients is unknown.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when EXTAVIA is administered in combination with agents that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance. Additional caution should be exercised with any co-medication which has an effect on the hematopoetic system.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

FOR SUBCUTANEOUS USE ONLY

EXTAVIA (interferon beta-1b) should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of multiple sclerosis.

Recommended Dose and Dosage Adjustment

The recommended dose of EXTAVIA for both relapsing-remitting and secondary-progressive MS patients is 0.25 mg (8 MIU) injected subcutaneously every other day. Limited data regarding the activity of a lower dose in relapsing-remitting MS are presented in the **CLINICAL TRIALS** section in Product Monograph (https://www.novartis.ca/en/our-products/pharmaceuticals).

Dose titration was used at the start of treatment in the clinically isolated syndrome and secondary-progressive MS studies in order to increase the tolerability of EXTAVIA.

In the study in patients with a single clinical event suggestive of MS (clinically isolated syndrome), dosage was increased as shown in **Table 5**.

Table 5: Schedule for Dose Titration[a]

Treatment Day	Dose	Volume
1, 3, 5	0.0625 mg (2 MIU)	0.25 mL
7, 9, 11	0.125 mg (4 MIU)	0.5 mL
13, 15, 17	0.1875 mg (6 MIU)	0.75 mL
≥ 19	0.250 mg (8 MIU)	1.0 mL

a Titration scheme as used in the study in patients with a single clinical event suggestive of multiple sclerosis. The titration period may be adjusted if any significant adverse reaction occurs.

In the secondary-progressive MS study, patients initiated treatment with half the dose (4 MIU s.c. every other day) for a period of 2 weeks prior to escalating to the recommended dose of 8 MIU (s.c. every other day).

Duration of treatment: Efficacy of treatment for longer than 2 years has not been substantially demonstrated in relapsing-remitting multiple sclerosis. For secondary-progressive multiple sclerosis, safety and efficacy data beyond 3 years are not available.

In patients with a single clinical event suggestive of MS, efficacy has been demonstrated over a period of three years.

Missed Dose

If an injection is missed, it should be given as soon as feasible. The next injection should be given two days later.

Administration

The removable rubber cap of the diluent (0.54% Sodium Chloride Solution) pre-filled syringe contains natural rubber latex and should not be handled by persons sensitive to this substance.

Reconstitution: To reconstitute lyophilized EXTAVIA for injection, use the vial adapter to inject the entire contents of the prefilled diluent syringe containing Sodium Chloride 0.54% Solution into the EXTAVIA vial. Gently swirl the vial of EXTAVIA to dissolve the drug completely; do not shake. Do not use cracked vials. Inspect the reconstituted product visually and discard the product before use if it contains particulate matter or is discolored. After reconstitution with diluent, each mL of solution contains 0.25 mg (8 MIU) interferon beta-1b, 13 mg Albumin Human USP and 13 mg Mannitol USP.

Vial Content	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
0.3 mg interferon beta-1b	1.2 mL	1.2 mL	0.25 mg/mL

Subcutaneous injection: Withdraw 1 mL of reconstituted solution from the vial back into the syringe, fitted with a ½-inch needle, and inject the solution subcutaneously. For dose titration at

the start of treatment draw the respective volume as given in **Table 5** above. Sites for self-injection include arms, abdomen, buttocks and thighs. All components are suitable for single use only; unused portions should be discarded (see **PART III: CONSUMER INFORMATION, PROPER USE OF THIS MEDICATION** section for self-injection procedure.)

STORAGE AND STABILITY

Before reconstitution

Store between 2 - 25°C. Excursions between 25°C and 30°C are permitted as long as they do not exceed a maximum of 30 days. Do not freeze. Do not use beyond the expiration date indicated on the labels of the EXTAVIA vial and the prefilled diluent syringe.

After reconstitution

The reconstituted product contains no preservative. If not used immediately, store under refrigeration between 2ºC and 8ºC (36ºF and 46ºF) **and use within 3 hours of reconstitution.** Do not freeze.

DOSAGE FORMS, COMPOSITION AND PACKAGING

EXTAVIA (interferon beta-1b) is presented in single-use vials of lyophilized powder containing 0.3 mg (9.6 MIU) interferon beta-1b, 15 mg albumin human USP and 15 mg mannitol USP. A pre-filled single-use syringe containing 1.2 mL of diluent (Sodium Chloride, 0.54% solution) is included for each vial of drug. The rubber cap of the diluent (0.54% Sodium Chloride Solution) pre-filled syringe contains natural rubber latex.

EXTAVIA is supplied in:

- Cartons containing 15 vials of medication and 15 prefilled diluent syringes (each containing 1.2 mL of Sodium Chloride 0.54% solution), to be used with the ExtaviPro® 30G Application Kit (supplied separately), which contains alcohol wipes (50), vial adapters (16), and 30 gauge needles (18), to prepare and inject EXTAVIA.

  The product supplied in cartons containing vials and pre-filled syringes can only be used with the ExtaviPro® 30G Auto-Injector.

PART III: CONSUMER INFORMATION

PrEXTAVIA®
Interferon beta-1b

Product supplied in cartons containing vials and pre-filled diluent syringes (to be used with the ExtaviPro® 30G Application Kit)

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

ABOUT THIS MEDICATION

What the medication is used for:
EXTAVIA is used for the treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations in ambulatory patients (i.e., patients who are able to walk without help).

EXTAVIA is also used for the treatment of secondary-progressive multiple sclerosis to slow the progression of disability and to reduce the frequency of clinical exacerbations.

EXTAVIA 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 that 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.

EXTAVIA 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 EXTAVIA works in MS is unknown. EXTAVIA 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:
You should NOT use EXTAVIA:

- if you have had previous allergic reactions, such as difficulty breathing, itching, flushing or hives, to interferon beta or to any of the non-medicinal ingredients (see below).

What the medicinal ingredient is:
The active ingredient is interferon beta-1b.

What the non-medicinal ingredients are:
EXTAVIA powder: human albumin, mannitol
Diluent: sodium chloride, water for injection

What dosage forms it comes in:
EXTAVIA is formulated as a sterile, white to off-white powder which must be dissolved using the supplied diluent. Each single-use vial contains 0.3 mg (9.6 million international units [MIU]) of interferon beta-1b. The diluent syringe contains 1.2 mL of sodium chloride 0.54% solution.

The prepared solution for injection contains 0.25 mg (8.0 MIU) of interferon beta-1b per 1 mL.

WARNINGS AND PRECAUTIONS

BEFORE you use EXTAVIA, talk to your doctor if you have any of the following conditions:

- Depression, anxiety (feeling uneasy, nervous or fearful for no reason), or trouble sleeping
- Liver problems
- Epilepsy or a history of seizures
- Heart problems
- Problems with your thyroid gland
- Are breast-feeding or are planning to become pregnant
- If you ever had an allergic reaction to rubber or latex. The rubber cap of the diluent pre-filled syringe contains natural rubber latex.

Depression: Some patients treated with interferons, including EXTAVIA, have become seriously depressed (feeling sad). Some patients have thought about or have attempted to kill themselves. 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 or healthcare provider as soon as possible. Your doctor may ask that you stop using EXTAVIA. Before starting EXTAVIA, you should also tell your doctor if you have ever had any mental illness, including depression, and if you take any medications for depression.

Allergic reactions: Some patients taking EXTAVIA have had severe allergic reactions leading to difficulty breathing and swallowing. Less severe allergic reactions such as rash, itching, skin bumps, or swelling of the mouth or tongue can also

happen. If you think you are having an allergic reaction, stop using EXTAVIA immediately and call your doctor.

Liver problems: EXTAVIA, like other interferon beta products, may cause severe liver problems. Some of the symptoms of liver problems are yellowing of the skin and whites of the eyes, malaise (a vague feeling of discomfort), fatigue, nausea, vomiting, abdominal pain, dark urine and itching of the skin. If you develop these symptoms while taking EXTAVIA, you should call your doctor right away.

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 EXTAVIA, you should call your doctor right away.

Heart problems: During treatment with EXTAVIA, cardiomyopathy (a disease of the heart muscle) has been reported. 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.

Thyroid problems: Some people taking EXTAVIA may develop changes in the function of their thyroid. Symptoms of these changes include feeling hot or cold much of the time or change in your weight (gain or loss) without a change in your diet or the amount of exercise you are getting.

Gastrointestinal problems: Inflammation of the pancreas has been observed with EXTAVIA use, often associated with an increase of triglycerides (a type of fat in the blood). If you have suffered from increased triglycerides or have had problems with your pancreas, please tell your doctor.

Women of childbearing potential: If you are a woman of childbearing potential and are taking EXTAVIA, 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 EXTAVIA. It is not known if interferons interfere with hormonal contraceptives.

Available data with the use of EXTAVIA in pregnant women (mostly during the first trimester) suggest that spontaneous abortions (miscarriage) and congenital abnormalities (malformations) in their children did not happen more often than in the general population. Spontaneous abortions (miscarriage) have been reported in patients with multiple sclerosis in clinical studies, however not more often than in the general population. Administration of doses that were higher than the dose normally used to treat patients with multiple sclerosis caused an increased rate of miscarriages in studies done in monkeys. However, when pregnancies in these studies were carried to term, the animals were born without malformations.

Breast-feeding: You should talk to your doctor if you are breast-feeding an infant. A decision should be made whether to stop breast-feeding or stop taking EXTAVIA.

Immune system problems: The administration of interferons to patients with a pre-existing rare disturbance of the immune system where abnormal proteins are found in the blood (monoclonal gammopathy) has been associated with problems with small blood vessels leading to shock (collapse) and, in some cases, death.

Human albumin: This product contains a protein (albumin) extracted from human blood and so carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of a disease affecting the nervous system (Creutzfeld-Jacob disease) is also considered extremely remote.

Kidney problems: 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 EXTAVIA 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), the use of EXTAVIA together with other substances that modify the immune system response was not studied. 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 non-prescription medicines, including vitamin and mineral supplements and herbal products.

PROPER USE OF THIS MEDICATION

EXTAVIA is intended for use under the guidance and supervision of a physician. Your physician or his/her delegate should instruct you in the preparation and self-injection technique of EXTAVIA. Do not begin your EXTAVIA treatment without training.

Usual dose:
EXTAVIA should be used as prescribed by your doctor. The usual dose is 1 mL of prepared EXTAVIA solution injected subcutaneously (under the skin) every other day. This is equal to 0.25 mg (8 MIU).

If you have been prescribed EXTAVIA because you have symptoms likely to be a first sign of multiple sclerosis, your treatment should be started at a low dose of 0.25 mL (0.0625 mg or 2 MIU). Your dose will then be increased slowly until you reach a dose of 1 mL. Your individual tolerability of EXTAVIA will determine the rate of dose increase. Your doctor will decide this with you.

Your injections should be about 48 hours (two days) apart, so it is best to take them at the same time each day, preferably in the evening before bedtime.

SELF-INJECTION PROCEDURE

SAFETY TIPS

- Use only the supplies that come with your EXTAVIA package and with the ExtaviPro® 30G Application Kit.
- Use only the diluent from the prefilled syringe.
- The removable rubber cap of the diluent prefilled syringe contains natural rubber (latex), which should not be handled by persons sensitive to this substance.
- Wash your hands thoroughly with soap and water before starting.
- Keep the items sterile. Do not touch the needle, the piercing spike of the vial adapter or the top of the cleaned vial.
- Make sure none of the items in your package have been opened or are damaged.
- Do not use after the expiry date shown on the EXTAVIA vial and the prefilled diluent syringe.
- Do not reuse opened materials. Throw away any unused portions of EXTAVIA and diluent.
- Throw away used syringes and needles in the proper disposal container.

Before preparing your injection of EXTAVIA, make sure you read the instructions below on how to choose an injection site and on what supplies you will need to get ready to give your injection.

CHOOSING AN INJECTION SITE

EXTAVIA should be injected into subcutaneous tissue (under the skin, between the fat layer and the muscles beneath). The best areas for injection are loose and soft, away from joints.

- Choose an injection site from the following areas (Figure 1):
  - A Right arm, upper back portion (at least 10-15 cm below the shoulder and 10-15 cm above the elbow)
  - B Left arm, upper back portion (at least 10-15 cm below the shoulder and 10-15 cm above the elbow)
  - C-D Abdomen, above the waistline (at least 5 cm on either side of the navel)
  - E Right thigh (at least 5 cm above the knee and 5 cm below the groin)
  - F Left thigh (at least 5 cm above the knee and 5 cm below the groin)
  - G Left buttock (upper, outer portion)
  - H Right buttock (upper, outer portion)
- Change injection areas every time you inject yourself. Give the site time to recover from the last injection. This will help prevent injection site reactions.
- Wait at least one week before reusing an area.
- Do not use any areas where you feel lumps, depressions, pain or discoloration; talk to your doctor or nurse about anything you find.

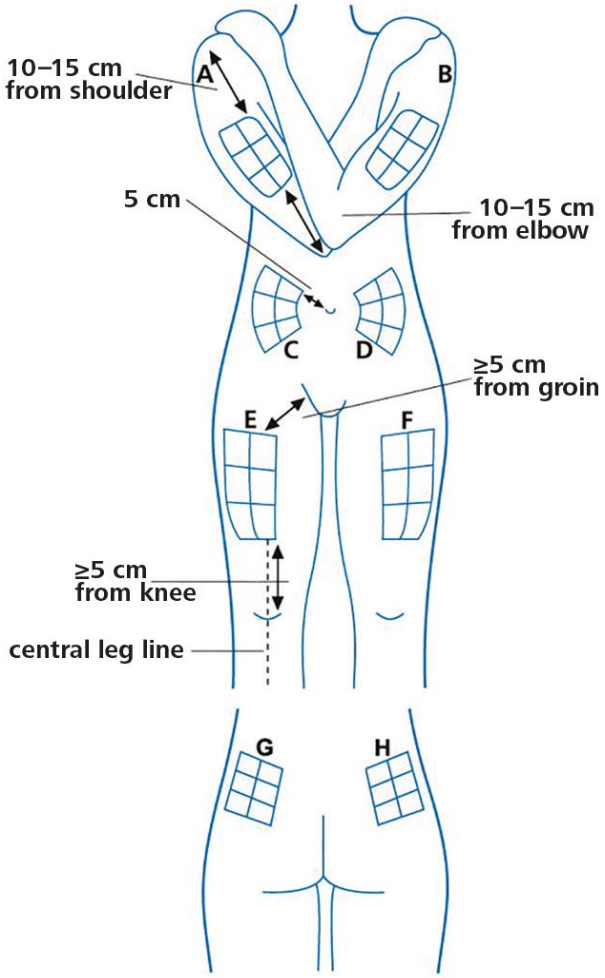


Figure 1

- Keep a record of when and where you are giving yourself injections. Use the EXTAVIA diary in your training kit.

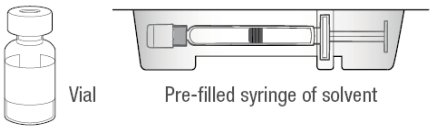
GATHERING YOUR SUPPLIES

EXTAVIA is supplied in cartons containing vials of medication and prefilled diluent syringes (‘**drug pack**’). To reconstitute and inject your medicine, you will also need an **application kit** for the administration of EXTAVIA (supplied separately from your medicine), which contains alcohol wipes, vial adapters,

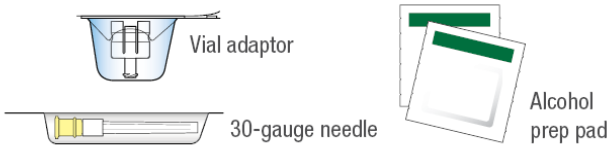
and 30 gauge needles.

You will need the following supplies to get ready to give your injection of EXTAVIA:

- **From the EXTAVIA drug pack, you will need:**
  - A vial of EXTAVIA
  - A prefilled diluent syringe



- **From the ExtaviPro® 30G Application Kit, you will need:**
  - Two (2) alcohol wipes
  - A vial adapter
  - A 30 gauge needle



RECONSTITUTING EXTAVIA AND PREPARING THE INJECTION

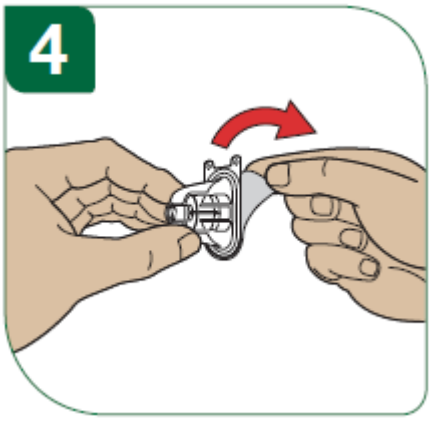
Step 1: Wash your hands thoroughly with soap and water before beginning this process.

Step 2: Remove the flip off cap from the EXTAVIA vial. It is best to use your thumb rather than your nail, as your nail could break.

Put the vial on the table.

Step 3: Clean the top of the vial with an alcohol wipe, moving the wipe in one direction only.

Leave the wipe on top of the vial.

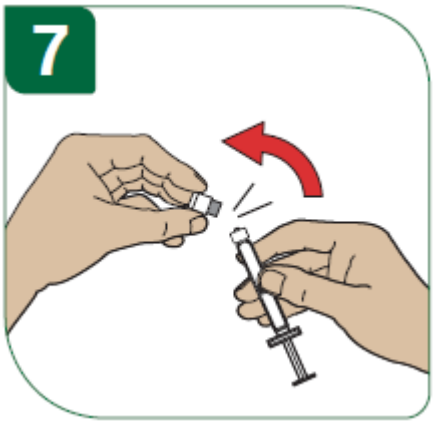


Step 4: Peel back and remove the cover from the vial adapter packaging. **Do not remove the vial adapter from its packaging.**

Note: Be sure to avoid touching the vial adapter, in order to maintain its sterility.

Step 5: Remove the wipe from the top of the vial. Use the packaging to handle the vial adapter. Attach it to the vial by pushing down until the vial adapter penetrates and locks around the top of the vial.

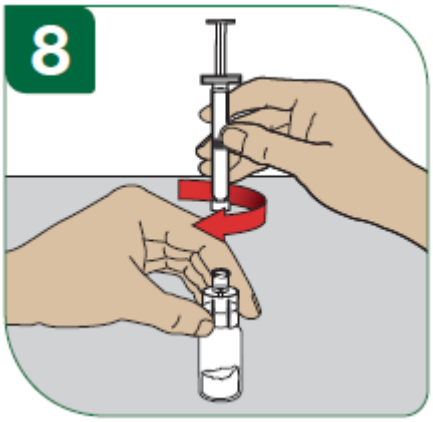
Step 6: Holding the edges securely, remove and discard the packaging **ensuring the vial adapter remains on the vial.**



Step 7: Take out the pre-filled diluent syringe from its packaging.

Snap off and discard the tip of the syringe.

Note: Be careful not to touch the exposed end of the syringe. Do not push the plunger.



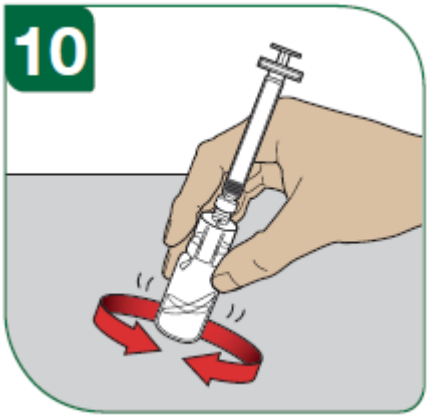
Step 8: Holding the vial and adapter securely, screw the syringe fully onto the vial adapter.

This forms the syringe-vial assembly.

Step 9: Hold the syringe-vial assembly at a slight angle. Push the plunger down slowly so that the liquid runs down the inside of the vial.

Transfer **all** of the diluent into the vial.

Note: Do not shake the vial as this may cause excessive foaming.

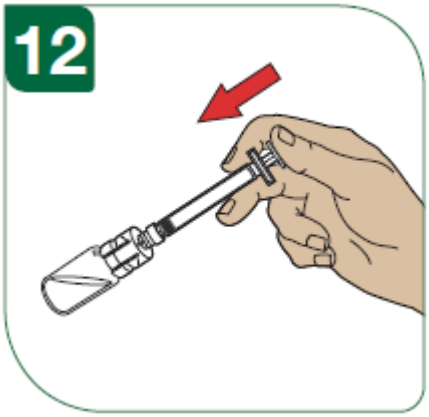


Step 10: Hold the vial between your thumb and fingers. Swirl the syringe-vial assembly gently until the powder is completely dissolved.

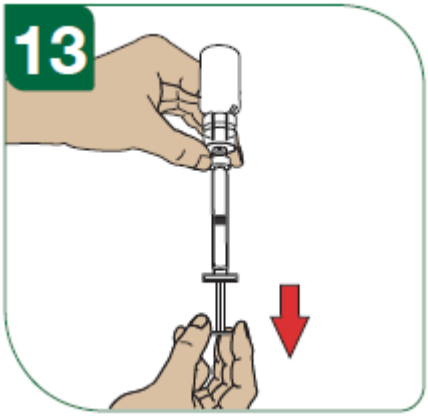
Note: Do not shake the vial.

Step 11: Examine the solution carefully. It should be clear and contain no particles.

Note: If the solution is discolored or contains particles, discard it and start again with a new syringe and vial out of your package. If excessive foaming is present – which can happen if the vial is shaken or swirled too vigorously – let the vial sit undisturbed until the foam settles.

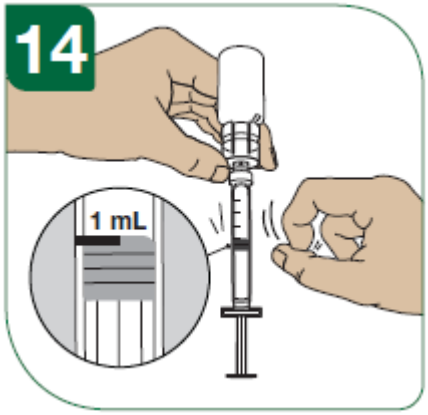


Step 12: Ensure the plunger stays fully pushed in before proceeding to the next step, as it may have moved.



Step 13: Turn the syringe-vial assembly so that the vial is at the top. Slowly pull the plunger back to draw all of the solution into the syringe.

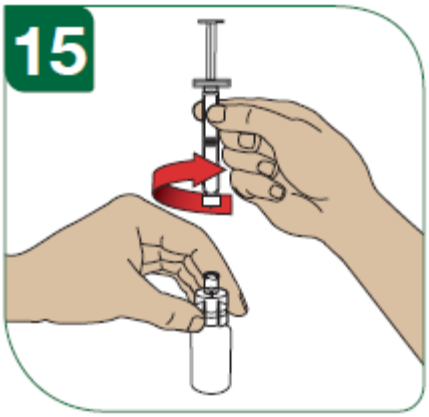
Note: If 1 mL of clear solution cannot be withdrawn from the vial, discard the vial and syringe and start over.



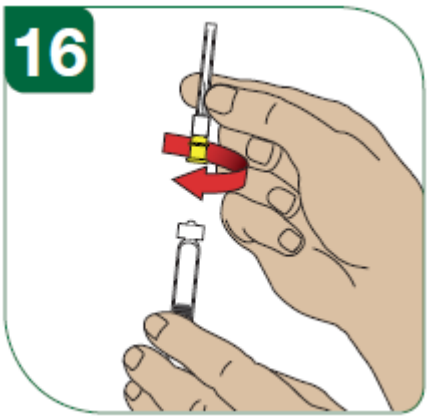
Step 14: Remove any excess air bubbles by gently tapping the syringe. Do not tap the syringe with a hard object because the syringe is made of glass and it could break

Push the plunger to the 1 mL mark on the syringe (or the volume prescribed by your doctor).

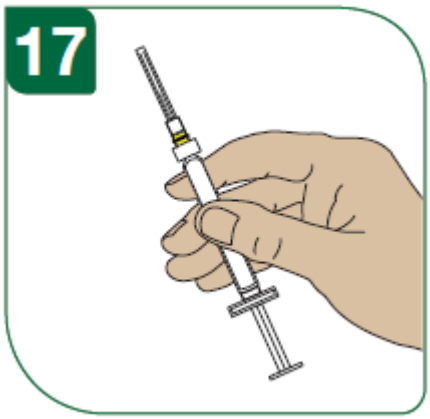
Note: It may be necessary to adjust the plunger position back and forth a few times to ensure the excess air bubbles are gone and there is 1mL of solution in the syringe.



Step 15: Unscrew the syringe, leaving the vial adapter on the vial.



Step 16: Take the needle out of its wrapping and screw it firmly onto the top of the syringe.



Step 17: Leave the needle cap on. You are now ready to inject.

The injection should be administered immediately after mixing. If you are unable to give the injection immediately, you may refrigerate the medication in the syringe and inject within three hours. Do not freeze.

INJECTING EXTAVIA

Optional - Autoinjector: If you have been given an autoinjector, you should follow the detailed instructions that are supplied with it. **Be sure to only use the ExtaviPro® 30G Auto-Injector.**

1. Use a fresh alcohol wipe to **clean** the skin at the injection site. Use a circular motion from the center of the injection site outward. Let the alcohol dry.

2. **Throw away** the wipe.

3. **Remove** the protective needle guard from the needle by pulling it without turning.

4. Gently **pinch** the skin around the site to lift it up a bit.

5. **Stick** the needle straight into the skin at a 90° angle with a quick, firm motion.

6. **Inject** the drug by using a slow, steady push (push the plunger all the way in until the syringe is empty).

7. **Remove** the needle from the skin.

8. Gently **massage** the injection site with a clean, dry cotton ball, gauze, or with a fresh alcohol wipe from your Application Kit (or as directed by your healthcare professional).

9. **Throw away** the syringe in the disposal unit.

10. **Discard** all other components.

Overdose:
If you accidentally take more than your prescribed dose, or take it two days in a row, call your doctor right away.

Missed Dose:
If you miss a dose, you should take your next dose as soon as you remember or are able to take it. Your next injection should be given about 48 hours (two days) after that dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with any prescription medication, side effects related to therapy can occur. Consult your doctor if you have any problems, whether or not you think they may be related to EXTAVIA.

Skin reactions: Injection site reactions are common. They include redness, pain, swelling and discoloration. Less frequently, injection site necrosis (skin breakdown and tissue destruction) has been observed. To minimize the chance of a reaction, change injection areas every time you inject yourself and wait at least one week before reusing an area. Do not inject into skin that is tender, red, or hard. Do not use any areas where you feel lumps, depressions, pain, or discoloration. Injection site reactions may occur less frequently if you use an autoinjector. Talk to your doctor or nurse about anything you find. If you experience a break in the skin or drainage of fluid from the injection site, consult your doctor. The occurrence of injection site reactions decreases over time.

Flu-like symptoms: Flu-like symptoms are also common. They include fever, chills, sweating, fatigue, and muscle aches. For many patients, these symptoms will lessen or go away over time. Taking EXTAVIA at night may help lessen the impact of flu-like symptoms. You should talk to your doctor about whether you should take an over-the-counter medicine for pain or fever reduction before or after taking your dose of EXTAVIA.

Liver problems: Your liver function may be affected. Elevations of liver function values occurred very commonly in patients treated with EXTAVIA in clinical studies and in most cases were mild and transient. Rare cases of severe liver injury have been reported (see WARNINGS AND PRECAUTIONS – Liver Problems).

Blood problems: A decrease of infection-fighting white blood cells, red blood cells, or platelets (cells that help you form blood clots) may occur. If decreases are severe, they can lessen your ability to fight infections, make you feel tired or sluggish or cause you to bruise or bleed easily.

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

Symptom / Effect		Talk with your doctor or pharmacist in all cases	Stop taking drug and call your doctor or pharmacist
Very common	Fluid retention (swelling) in ankles or legs	✓	
Common	Break in skin or drainage of fluid at injection site	✓	
	Rash	✓	
Uncommon	Difficulty breathing or swallowing, swelling of mouth or tongue		✓
	Depression or suicidal thoughts	✓	
	Seizures	✓	
	Symptoms of liver problems: yellowing of the skin and whites of eyes, malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, itching of the skin	✓	
	Symptoms of kidney problems: foamy urine, fatigue, swelling, particularly in the ankles and eyelids, and weight gain	✓	

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

HOW TO STORE IT

Before reconstitution: Store EXTAVIA between 2 - 25°C. Excursions between 25°C and 30°C are permitted as long as they do not exceed a maximum of 30 days. Do not freeze.

After reconstitution: If not used immediately, reconstituted EXTAVIA must be refrigerated and used within three hours. Do not freeze.

Keep syringes and needles away from children. Do not reuse needles or syringes. Discard used syringes and needles in a syringe disposal unit.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca
By regular mail: National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

http://www.novartis.ca

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc.at:

1-800-363-8883

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